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The second truism is that women whose vanity will not permit them to wear any kind of white lenses will wear dark green lenses, even in the home and in night clubs. High myopes who cannot recognize their friends on the street won't wear glasses unless they are sunglasses.

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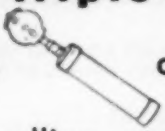
diagnostic triple-threat the world's largest selling  ophthalmoscope, and the world's largest selling otoscope fitted in a case that's truly sanitary and amazingly durable . . . that's the new . . .

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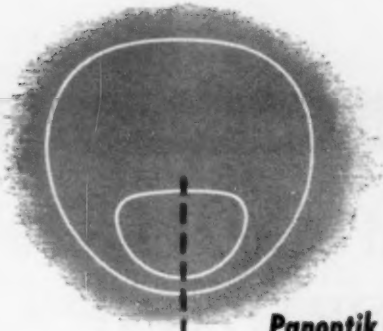

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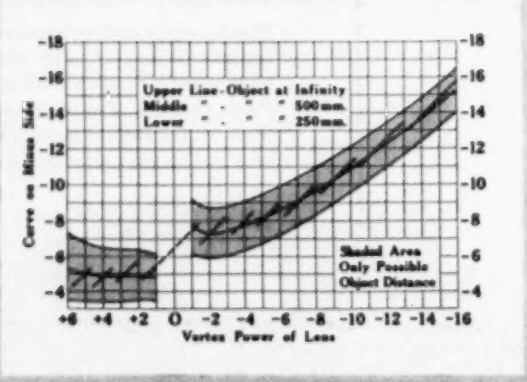

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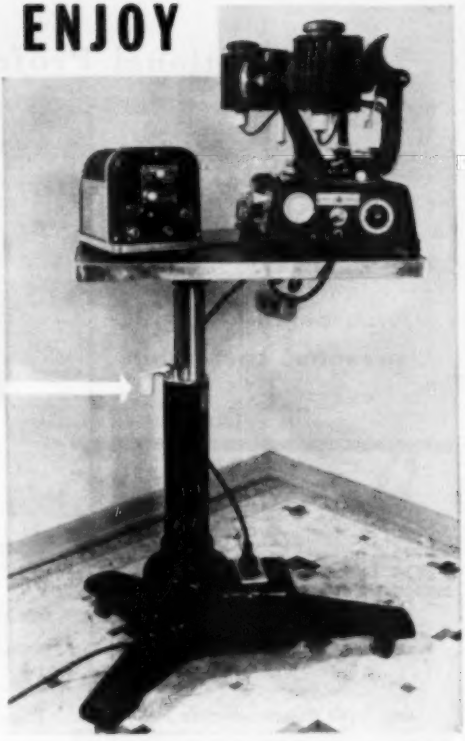

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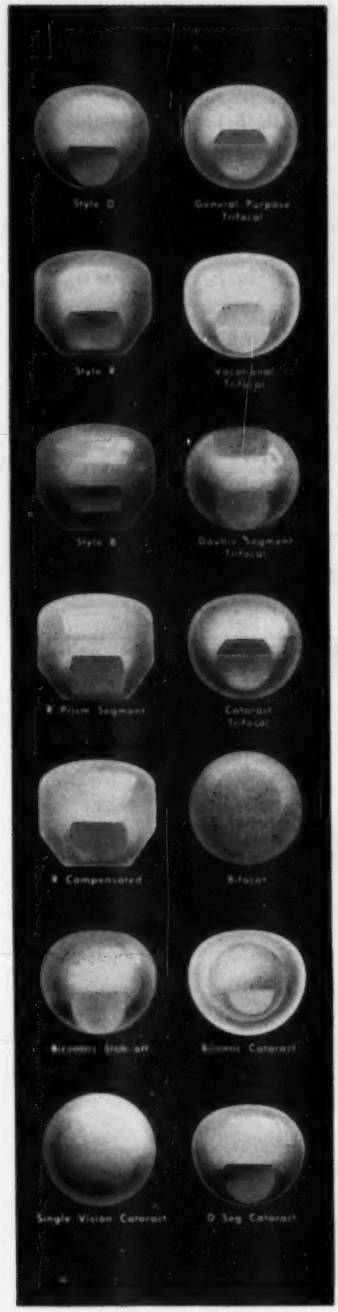

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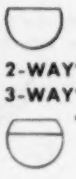

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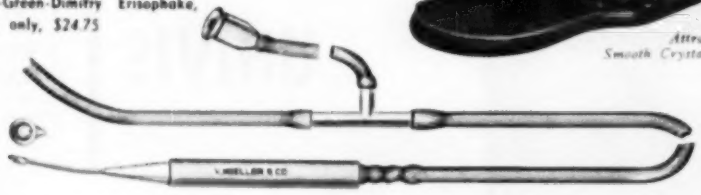

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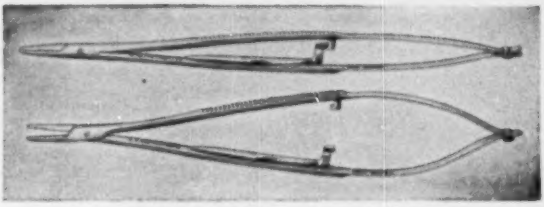

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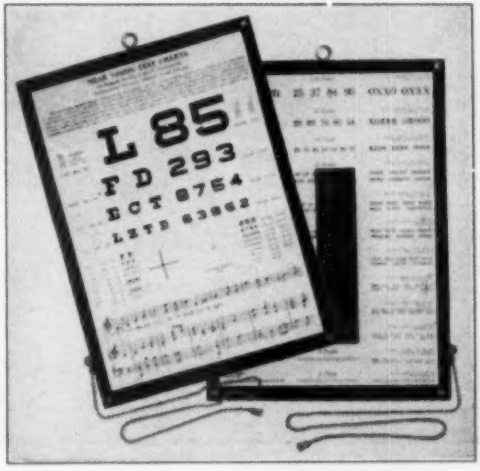

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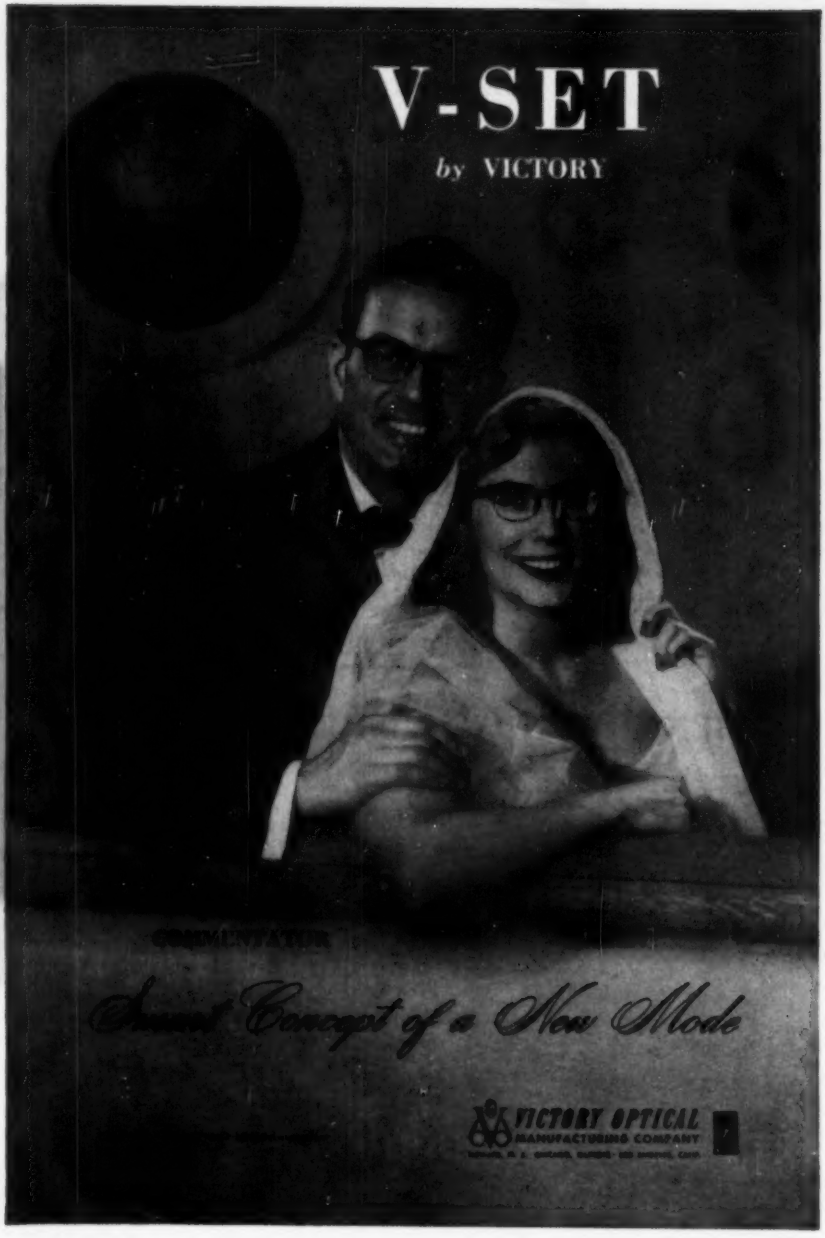
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PSEUDOGLAUCOMA

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AND
HAROLD G. SCHEIE, M.D.
PHILADELPHIA

DURING the past two years, all patients with glaucoma at the Hospital of the University of Pennsylvania have been transferred from the general ophthalmic clinics to a special glaucoma clinic. At the time of transfer each patient's record was carefully reviewed and the type of glaucoma was determined as accurately as possible. We were impressed at finding some patients who had been treated for glaucoma for years, when, in reality, they had an ocular condition which only simulated that disease. All this group of patients had normal ocular tension but showed cupping of the nerve head and visual field defects compatible with glaucoma. The subject of pseudoglaucoma, or "glaucoma without hypertension," "low tension glaucoma," "soft glaucoma" or "relative glaucoma," has evoked lively discussion in the European literature, with two recent excellent reviews by Dalsgaard-Nielsen and Sjögren [1]; but because there have been relatively few reports in the American literature, it seemed worth while to submit the present review, together with a report of our cases.

HISTORICAL REVIEW

The concept of "glaucoma without hypertension" was introduced in the 1850's, at about the time that the glaucomatous cup was recognized and it was becoming universally known that ocular hypertension was the cardinal symptom of glaucoma.

Only two years after the description of the excavated disk in glaucoma by Weber,[2] in 1855, von Graefe [3] (1857) suggested that cupping

From the Department of Ophthalmology, Hospital of the University of Pennsylvania and the University of Pennsylvania School of Medicine.

1. (*a*) Dalsgaard-Nielsen, E.: Glaucoma-like Cupping of the Optic Disc and Its Etiology, Acta ophth. **15**:151, 1937. (*b*) Sjögren, H.: A Study in Pseudoglaucoma (Glaucoma Without Hypertension), ibid. **24**:239, 1946.

2. Weber, A.: Ein Fall von partieller Hyperämie der Chorioidea bei einem Kaninchen, Arch. f. Ophth. **2**(pt. 1):133, 1855.

3. von Graefe, A.: Über die Iridectomie bei Glaucom und über den glaucomatösen Process, Arch. f. Ophth. **3**:456, 1857.

may occur with no increase in tension. This he called "amaurosis with excavation." This suggestion provoked considerable controversy, although at the time ocular tension was determined only by palpation. Most ophthalmologists, however, agreed with Donders [4] that increased tension must be present for cupping to occur. They expressed the opinion that in von Graefe's cases of amaurosis with excavation the rise in tension must have been present, though slight. Indeed, in a later paper, von Graefe [5] modified his view and recognized his amaurosis with cupping as a mild form of glaucoma. From then until Schiötz described his tonometer, in 1905,[6] it was believed, with rare exceptions, that all cupping of the disk must be glaucomatous.

After the tonometer was introduced and it became possible to measure even small changes in tension with fair accuracy, reports began to appear once again of cases with cupping of the disk in which no increase in tension could be shown.[7] Virtually every author advanced a new theory to explain the cupping in the presence of normal tension. One of the earliest explanations was that offered by de Wecker [8] and Elschnig,[9] who both stated that the excavation was due to primary optic nerve atrophy superimposed on a deep physiologic cup. Schnabel [10] stated the belief that the excavation which occurred both in glaucomatous eyes and

4. Donders, cited by Haffmans, J. H. A.: Beiträge zur Kenntnis des Glaucoma, Arch. f. Ophth. **8**(pt. 2):124, 1861-1862.

5. von Graefe, A.: Über die glaucomatöse Natur der "Amaurosen mit Sehnervenexcavation" und über das Wesen and die Classification des Glaucoms, Arch. f. Ophth. **8**(pt. 2):271, 1862.

6. Schiötz, H.: Ein neuer Tonometer: Tonometrie, Arch. f. Augenh. **52**:401, 1905.

7. (*a*) Stock, W.: Über die mit dem Tonometer von Schiötz gewonnenen Resultate bei normalen und glaucomatösen Augen: besonders vor und nach den verschiedenen druckherabsetzenden Operationen, Klin. Monatsbl. f. Augenh. (supp.) **48**(pt. 2):124, 1910. (*b*) Lauber, H.: Statement made at a meeting of the Ophthalmological Society of Vienna, October 1910, Ztschr. f. Augenh. **25**:110, 1911. (*c*) Morax, V.: Glaucome simple ou atrophie avec excavation, Ann. d'ocul. **153**:25, 1916. (*d*) Kayser, B.: Primäre lakunare Atrophie des N. opticus oder Glaukomexkavation, Klin. Monatsbl. f. Augenh. **66**:923, 1921. (*e*) Aubineau, E.: Le faux glaucome, Ann. d'ocul. **167**:550, 1930. (*f*) Fuchs, A.: On Pseudoglaucoma, Brit. J. Ophth. **12**:65, 1928. (*g*) Reid, A. C.: Atrophic Recession of the Lamina Cribrosa, ibid. **21**:361, 1937. (*h*) Gradle, H. S.: Glaucoma Simplex Without Perceptible Rise in Tension, Arch. Ophth. **46**:117, 1917. (*i*) Pickard, R.: Cavernous Optic Atrophy and Its Relation to Glaucoma, Brit. J. Ophth. **9**:385, 1925.

8. de Wecker, L.: Traité théorétique et pratique des maladies des yeux, Paris, A. Delehaye, 1863-1867, p. 608.

9. Elschnig, A.: Die Topographie des Schnerveneintrittes bei einfacher Schnervenatrophie, Arch. f. Ophth. **68**:126, 1908.

10. Schnabel, J.: Die Entwicklungsgeschichte der glaukomatösen Exkavation, Ztschr. f. Augenh. **14**:1, 1905.

in eyes with normal tension was due to primary cavernous atrophy of the optic nerve. Pickard,[11] in several papers on this subject, agreed with Schnabel. Sjögren [11b] further suggested that similar primary lacunar degeneration may occur in the brain, as well as in the optic nerve.

Fuchs [11] presented a theory that is still popular. He suggested that a poorly developed lamina cribrosa might give way against even normal intraocular tension, so that a state of "relative glaucoma" would exist at the nerve head. Such an eye was felt to be constructed to withstand only a pressure below that which is regarded as the physiologic normal. This was also the viewpoint expressed by Stock [12a] and Heilbrun,[12] who did much of the early clinical tonometric investigation in Axenfeld's and von Hippel's clinics, respectively.

In a later paper,[13] Elschnig advanced a second theory on the pathogenesis of cupping with normal tension, suggesting that the cupping was the result of the dissolution of the nerve fibers as an excess of intraocular fluid passed through them.

In the earliest report of "glaucoma without hypertension" that appeared in the American literature, Gradle [2b] stated that the cupping was a sequel of toxic neuritis. This suggestion seems particularly appropriate in view of the several reports of deep excavations after methyl alcohol poisoning that have appeared in the American literature.[14]

Finally, the papers of Thiel [15] and Knapp [16] have suggested, on the basis of roentgenologic evidence, that pressure on the optic nerve by calcified carotid arteries may be the basis of pseudoglaucoma. At present this concept of pseudoglaucoma is widely accepted in spite of some disagreement, which will be discussed further in this paper.

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11. Fuchs, E.: Discussion at meeting of Ophthalmological Society of Vienna, October 1910, Ztschr. f. Augenh. **25**: 108, 1911; Über die Lamina cribrosa, Arch. f. Ophth. **91**:435, 1916.

12. Heilbrun, K.: Über bisher mit dem Schiøtzschen Tonometer erzielte Resultate, Arch. f. Ophth. **79**:256, 1911.

13. Elschnig, A.: Glaukom ohne Hochdruck und Hochdruck ohne Glaukom, Ztschr. f. Augenh. **52**:287, 1924.

14. Gruening, E.: Methyl Alcohol Amblyopia: Clinical Records and Historical Study, Arch. Ophth. **39**:333, 1910. Friedenberg, P.: The Nervehead in Wood-Alcohol Amaurosis, Tr. Am. Ophth. Soc. **12**:513, 1910. Morrison, F.: Glaucomatous Cupping with Low Ocular Tension After Wood Alcohol Poisoning, Am. J. Ophth. **5**:644, 1922. Shannon: A Case of Bilateral Optic Atrophy Due to Methyl Alcohol Poisoning, Arch. Ophth. (May) **7**:813, 1932.

15. Thiel, R.: Glaukom ohne Hochdruck, Ber. u. Versamml. d. deutsch. ophth. Gesellsch. **48**:133, 1930.

16. *(a)* Knapp, A.: On the Association of Sclerosis of the Cerebrobasal Vessels with Optic Atrophy and Cupping, Tr. Am. Ophth. Soc. **30**:343, 1932; *(b)* Course in Certain Cases of Atrophy of the Optic Nerve with Cupping and Low Tension, Arch. Ophth. **23**:41 (Jan.) 1940.

More recently, diagnostic procedures have been developed in an attempt to diagnose glaucoma before the classic triad of hypertension, atrophic cupping and field defects becomes evident. Thus, Löhlein [17] called attention to the variation of the ocular tension at different times of the day and to the necessity for repeated and systematic tonometric studies. A host of provocative tests have been described.[18]

The cases of "glaucoma without hypertension" were then further studied by these diagnostic procedures. A notable contribution is the paper of vom Hofe,[19] who systematically studied 223 cases with cupped disks and usually low tensions. On the basis of early morning tensions or positive results of provocative tests, an elevated tension was found at some time in all but two cases. Vom Hofe therefore concluded that cupping of the disk in truly nonglaucomatous patients must be a rare phenomenon. Nonetheless, though rare, there do exist cases with deeply cupped disks in which no rise of tension can be demonstrated at any time. In some of these the cause of the cupping and atrophy is still open to speculation. A popular theory today is that of Fuchs, namely, that a weakened lamina cribrosa gives way to "normal" ocular tension, so that a state of "relative glaucoma" exists. However, there are other cases in which a definite cause could finally be established. It is this group that we wish to review.

ESTABLISHED CAUSES OF PSEUDOGLAUCOMA

A. Tumors.—A clearly proved, but extremely rare, cause of pseudoglaucoma is a tumor arising near the optic chiasm. Only five such cases were found in the literature.

Hamann [20] reported the case of a woman aged 54 whose complaints were primarily visual. She had been treated for glaucoma by an ophthalmologist for three years and had had successful bilateral corneoscleral trephinations. The preoperative ocular tension was not given in the report, but the postoperative tension was normal when Hamann saw her. In spite of this, progressive loss of the visual fields had occurred after operation. Roentgenograms of her skull were therefore taken, and these showed massive erosion of the sella turcica. It is possible that the two diseases coexisted, although the progressive loss of visual field following successful trephinations speaks against this.

17. Löhlein, W.: Die Druckkurve des glaukomatösen Auges in ihrer Bedeutung für Diagnose, Prognose und therapeutische Indikationstellung, Klin. Monatsbl. Augenh. (supp.) **77**:1, 1926.

18. Duke-Elder, W. S.: Text-Book of Ophthalmology: Diseases of the Inner Eye, vol. 3, St. Louis, C. V. Mosby Company, 1941, 3389.

19. vom Hofe, K.: Klinisches über die glaukomatöse Exkavation ohne Drucksteigerung, Arch. f. Augenh. **100-101**:414, 1929.

20. Hamann, J.: Beitrag zur Diagnose und Therapie von Hypophysentumoren, Ztschr. f. Augenh. **68**:317, 1929.

In 1930 Thiel [15] presented the case of a man aged 79 who had previously had bilateral Elliot trephinations and was being continued on a pilocarpine regimen because of progressive loss of field. Again, roentgenograms of the skull showed evidence of an intrasellar tumor.

Dalsgaard-Nielsen [16] added two more such cases in her fine review in 1937. One, that of a man aged 40, was characterized by pronounced cupping, but normal ocular tension, which was not influenced in provocative tests. A roentgenogram showed enormous enlargement of the sella. A spongioblastoma of the hypothalamus was subsequently found at operation. In the second case, that of a woman aged 57, the diagnosis of glaucoma had been made on the basis of cupping and a quadrantic nasal field loss in her left eye. Ocular tension was normal. Again, a roentgenogram showed destruction of the sella, and roentgen therapy was given.

In the fifth case, that of Möller,[21] there were not only excavated disks, but even bilateral nerve fiber bundle defects. The tension was normal and uninfluenced by provocative tests. An enlarged sella was demonstrated roentgenologically. Operation revealed the tumor to be a chordoma of the clivus.

It seems of importance that in three of the five cases just reviewed treatment for glaucoma was given despite normal ocular tensions. Progressive loss of field occurred in all while the patients were on an antiglaucoma regimen, before the proper diagnosis was made. Ordinarily, one rarely thinks of tumor when nerve fiber bundle defects are found, though Traquair has mentioned this possibility.[22]

B. Congenital Anomalies.—A second group of cases in which glaucoma-like cupping of the disk may be noted, often associated with visual field defects, is that of congenital anomalies. Scattered reports of such cases, in which the differential diagnosis of glaucomatous cupping and a congenital anomaly of the disk was considered, are found in the literature.[22a] In at least two of these cases,[23] a diagnosis of glaucoma was made; the patient was kept under treatment with miotics and followed for some years, and surgical intervention was advised.

21. Möller, H. U.: Symptômes, simulant le glaucome, dans un chordome du Clivus Blumenbachii, Acta ophth. **17**:20, 1939.

22. Traquair, H. M.: The Nerve-Fibre Bundle Defect, Tr. Ophth. Soc. U. Kingdom **64**:3, 1944.

22a. Schmidt-Rimpler, H.: Glaucom, in von Graefe, A., and Saemisch, T.: Handbuch der gesammten Augenheilkunde, Leipzig, W. Engelmann, 1874-1880, vol. 5, p. 50. Terrien, F., and Petit, P.: Excavation énorme congénitale de la papille, Arch. d'ophth. **21**:405, 1901. Zade, M.: Zwei eigenartige Fälle von kongenitaler Anomalie des Sehnerveneintritts, Klin. Monatsbl. f. Augenh. **45**:435, 1907. Rönne, H.: Pseudoglaukomatöse kolobomatose Exkavation der Papille, Arch. f. Ophth. **105**:465, 1921. Fuchs.[7f]

23. Stock.[7a] Szily, A.: Monographie des Sehnervenkopfes im menschlichen Auge, 1901; cited by Fuchs.[7f]

Congenital anomalies of the disk which may simulate glaucomatous cupping include an unusually oblique insertion of the optic nerve, branching of the vessels behind the lamina cribrosa, so that individual branches appear at the margins of the disk, and congenital coloboma of the optic disk. As a rule other congenital anomalies, such as coloboma of the choroid, high myopia or more obvious anomalous changes in the fellow eye, are present. In cases of coloboma in which the excavation lies entirely within the nerve sheath,[24] the diagnosis may be especially difficult.

C. Syphilitic Optic Nerve Atrophy.—It seems strange that there have not been more reports of cases in which glaucoma was confused with the optic nerve atrophy of tabes, and vice versa. Morax [25] emphasized the possibility of a syphilitic etiology in the "soft glaucomas." Lauber and Sobanski evidently considered the optic nerve atrophy of tabes as identical with pseudoglaucoma. In a long series of papers,[25] they attempted to show that disturbed nutrition of the optic nerve, due to disturbances in the interrelation of retinal arterial blood pressure and ocular tension, may be the basis of various ocular diseases. These statements, however, were presented without adequate substantiating evidence and failed to stand up to the effective critical analysis of Moore and Woods.[26] Sloan and Woods [27] stressed the fact that primary syphilitic atrophy of the optic nerve can cause various types of field defects. One of these is the sector-shaped, or nerve fiber bundle, defect oftenest associated with glaucoma.

D. Sclerosis of Carotid Arteries.—Sclerosis of the carotid arteries is considered by many to be the commonest cause of pseudoglaucoma. For many years degenerative changes had been known to occur in the optic nerves in association with sclerosis of the internal carotid arteries, but they had not been popularly associated with pseudoglaucoma until the papers of Thiel [15] and Knapp [16] (1932).

Earlier authors [28] had demonstrated cases having visual disturbances associated with sclerotic internal carotid arteries pressing on the optic nerves. Roentgenographic demonstration of calcification of the basal

24. Mann, I.: Developmental Anomalies of the Eye, London, Cambridge University Press, 1937, p. 124.

25. Lauber, H., and Sobanski, J., cited by Moore and Woods.[26]

26. Moore, J. E., and Woods, A. C.: The Pathology and Pathogenesis of Syphilitic Primary Optic Atrophy, Am. J. Ophth. **23**:1, 1940.

27. Sloan, L., and Woods, A. C.: Perimetric Studies in Syphilitic Optic Neuropathies, Arch. Ophth. **20**:201 (Aug.) 1938.

28. Türck: Sitzungb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. **9**:299, 1852; cited by Knapp.[16a] Knapp, H.: Jahresb. ü. d. Leistung. . . . d. Ophth. **6**:372, 1875; cited by Knapp.[16a] Otto, R.: Untersuchungen über Sehnervenveränderungen bei Arteriosclerose, Berlin, Julius Springer, 1893, p. 132. Liebrecht: Sehnerv und Arteriosclerose, Arch. f. Augenh. **44**:193, 1901.

vessels was made in the 1920's.[29] Horniker[30] was probably the first ophthalmologist to describe a case with the complete picture of an excavated disk, field cuts and normal ocular tension, and with calcified basal vessels demonstrated roentgenographically.

After Thiel's and Knapp's papers, sclerotic carotid arteries were generally accepted as a cause of "soft glaucoma." Within a few years six other papers appeared[31] describing cases in which the disks and field cuts resembled those in glaucoma, ocular hypertension was ruled out by repeated tonometric and provocative tests and roentgenologic evidence of calcification at the base of the brain was present.

After these papers, Thiel's thesis seemed to be based on firm ground, but his view did not go entirely unchallenged. In 1933 Saphir[32] presented six cases with autopsy showing pressure of sclerotic carotid arteries on the optic nerve. No "visual disturbances" had been recognized during life, and therefore Saphir felt it unlikely that such pressure from sclerotic vessels could often explain visual loss in elderly persons. However, no detailed examination of the visual fields had been made prior to the death of his patients.

More convincing are the papers of Glees[33] and Siegert.[34] These authors routinely roentgenographed the skulls of a series of consecutive patients over 50 years of age, regardless of the type of ocular disease. A considerable number showed calcifications at the base of the brain, the majority having neither cupping nor field defects. Glees therefore expressed doubt whether the roentgenographic findings had a direct causal relation to disease of the optic nerve. Siegert concluded that in the occasional patient having changes in the optic nerve associated

29. Pincherle: Über die röntgenographische Darstellung verkalkten Hirnarterien, Fortschr. a. d. Geb. d. Röntgenstrahlen. **29**:315, 1921; cited by Sjögren,[1b] Schüller: Röntgenpraxis, **2**:269, 1930; cited by Knapp.[16a]

30. Horniker: Ophth. Gesellsch., Heidelberg, 1924, p. 283; cited by Sjögren.[1b]

31. (*a*) Velhagen, K., Jr.: Sellabrücken, Arch. f. Augenh. **108**:559, 1934; (*b*) Zur Kasuistik der chiasmanahen Kalkschatten, Klin. Monatsbl. f. Augenh. **94**:586, 1935. (*c*) Kurz, O.: Zur Pathogenese des Glaukoms ohne Hochdruck, Arch. f. Augenh. **109**:108, 1935. (*d*) Ohm, G.: Glaukomproblem und Belastungsversuche: Das intermittierende Glaukom, Arch. f. Ophth. **135**:537, 1936. (*e*) Gasteiger, H.: Über den Wert der Röntgendiagnose bei unklaren Sehnervenleiden, Klin. Monatsbl. f. Augenh. **96**:589, 1936. (*f*) Elwyn, H.: Calcified Carotid Artery with Atrophy of the Optic Nerve, Cupping and Low Tension: Report of a Case, Arch. Ophth. **24**:476 (Sept.) 1940.

32. Saphir, O.: Changes of the Optic Nerve Resulting from Pressure of Arteriosclerotic Internal Carotid Arteries, Am. J. Ophth. **16**:110, 1933.

33. Glees, M.: Klinischer Beitrag zur Frage der chiasmanahen Kalkschatten bei Sehnerenveränderungen, Arch. f. Augenh. **110**:121, 1936.

34. Siegert, P.: Die ursächliche Bedeutung einer Verkalkung oder Thrombose der Carotis interna für Funktions-störungen des Auges, Arch. f. Ophth. **138**:798, 1938.

with sclerotic arteries the lesions were due to lack of nutrition rather than to direct compression of the nerve. Several other authors [35] have stated the opinion that the sclerotic nutrient vessels, rather than direct pressure, are responsible for the changes in pseudoglaucoma.

A recent paper of McLean's [36] offers an interesting suggestion as to the mechanism of the involvement of the optic nerve in these cases. His patient had "soft glaucoma," but there seemed sufficient evidence of a lesion at the base of the brain to warrant a craniotomy. The carotid arteries were found to have calcified plaques in their walls, just beneath the optic nerves. These plaques could be seen hammering against the nerves with each pulse beat. This condition was felt to be definite evidence, in the living patient, of the mechanism of injury to the optic nerves in this case.

As a whole, it seems that Thiel's theory, that the sclerotic carotid arteries bear a direct causal relation to the changes in the optic nerve, is an acceptable one. The precise mechanism of the injury may be open to some doubt.

REPORT OF CASES

In reviewing the histories of 150 patients transferred to the glaucoma clinic with the diagnosis of that disease in the past two years, a small group, previously treated for glaucoma, was found in whom no elevated tension could be demonstrated and yet they had visual field defects and cupping of the disk compatible with the diagnosis of glaucoma. After careful study, causes other than glaucoma were found in some cases, but in others an exact diagnosis has not as yet been made. A rather definite etiologic factor was discovered in the four cases to be reported.

CASE 1.—*Pituitary tumor.*

D. C., a Negro woman aged 65, first came to the ophthalmic clinic of the Hospital of the University of Pennsylvania in 1941 because of marginal keratitis. Her corrected vision was 6/9 in each eye. In the ensuing years she was seen several times for recurrent ulcer, with no visual change until May 1946. At this time the left disk appeared cupped. The central field of the left eye showed an arcuate scotoma, breaking through into the lower periphery (chart 1). Ocular tension was 22 mm. of mercury in the right eye and 25 mm. in the left eye (Schiøtz). A diagnosis of chronic simple glaucoma was made. Pilocarpine medication was started.

35. Best, F.: Die Hirnarteriosklerose und Hypertonie, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1931, vol. 6, p. 545. von Stief, A.: Zur Histopathologie des Sehnerven bei der Arteriosklerose und bei der senilen Demenz, Ztschr. f. Augenh. **70**:41, 1929. Kurz,[6c] Knapp,[16b] Rintelen, F.: Über arteriosklerotische Opticusatrophie, Ophthalmologica **111**:285, 1946. Vail, D.: The Blood Supply of the Optic Nerve and Its Clinical Significance, Am. J. Ophth. **31**:1, 1948.

36. McLean, J. M., and Ray, B. S.: Soft Glaucoma and Calcification of Internal Carotid Arteries, Arch. Ophth. **38**:154 (Aug.) 1947.

During the next two years all tension readings were in the low 20's. There was no further loss of visual field in the left eye, but the field in the right eye began to show an arcuate scotoma (chart 2). For this reason operation for glaucoma was considered, and the patient was admitted for studies.

Her ocular tension remained in the low 20's even after pilocarpine was stopped. Gonioscopic studies showed open angles, and the result of a water provocative test was negative. It was suggested that this type of field defect might be caused by

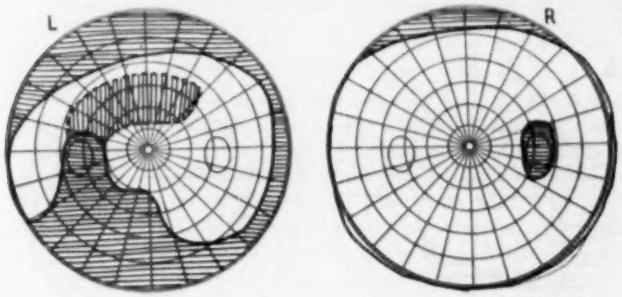

Chart 1 (case 1).—May 1946: Nerve fiber bundle defect in the left eye, with breaking through to the periphery below. Broken line shows field for 2/1000 white; solid line, field for 5/1000 white.

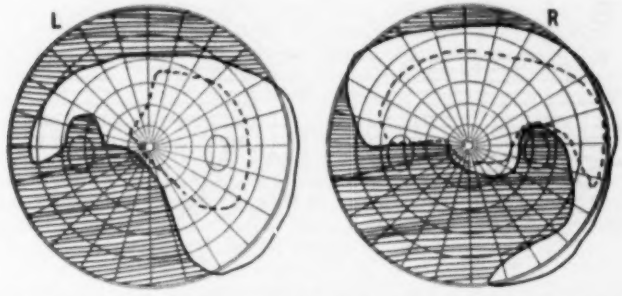

Chart 2 (case 1).—May 1948: The left eye shows no significant change, but the right eye now has an arcuate scotoma breaking through to the periphery. Broken line shows field for 2/1000 white; solid line, field for 5/1000 white.

a pituitary tumor, and a roentgenogram of the skull was taken. This showed enormous ballooning of the sella turcica and erosion of the clinoid processes. Roentgen therapy to the pituitary gland rather than surgical intervention was advised because of her age and relatively good visual acuity, and a total of 2,000 r was given.

The patient has been followed over a year since her course of radiation, and there has been no further loss in visual acuity or in field. No miotics have been used, and no increase in tension has been recorded.

Summary.—This patient was treated with miotics for two years on the basis of the presence of cupping of the disk and nerve fiber bundle defects, despite normal tension. Because of progressive loss of field, filtering operations were contemplated. Reevaluation for surgery led to the diagnosis of pituitary tumor, for which she received roentgen therapy. No further loss of field has occurred during the ensuing year. The cupping and loss of field were therefore attributed to pressure by the tumor on the optic nerves, rather than to a glaucomatous process.

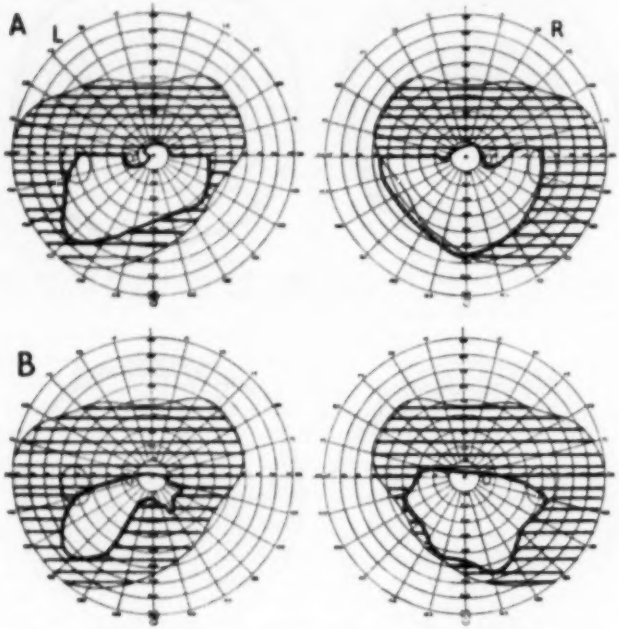

Chart 3 (case 2).—Peripheral fields (5/330), showing altitudinal defects, with loss of the upper half of the field (upper fields, October 1927; lower fields, August 1948). There has been virtually no change in the 20 years. Visual acuity was 6/150 in the right eye and 6/60 in the left eye, so that apparent sparing of macula in 1927 was an artefact.

Case 2.—*Congenital colobomas of the optic nerve.*

C. D., a Negro aged 32, was first seen in the ophthalmic clinic of the Hospital of the University of Pennsylvania in 1922 because of poor vision. His best visual acuity was 6/150 in the right eye and 6/60 in the left eye. The disks appeared deeply cupped, with the vessels apparently disappearing at the margins. Ocular tension was 32 mm. of mercury in the right eye and 26 mm. of mercury in the left eye (Schiötz). A field defect involved the upper half-field, including the macula, of each eye (chart 3).

Bilateral cyclodialyses were done in October 1922, and the patient has been using pilocarpine regularly since. He has been seen several times a year. Throughout these twenty-five years tension has run in the low 20's, and there has been no significant change in field or in visual acuity.

Because the patient had shown no changes over this period, he was presented at staff conference. It was felt that the changes in the disks were not due to glaucoma, but, rather, were bilateral colobomas, lying entirely within the optic nerve sheath. Use of miotics was therefore stopped, with no subsequent rise in tension. Gonioscopic studies showed open angles, with no functioning cyclodialysis clefts visible. Early morning tensions were normal. A water provocative test showed a borderline increase in tension of 9 mm. (to 30 mm.) in the right eye and no increase in tension in the left eye. A mydriatic test gave negative results.

Summary.—This man's disease was diagnosed as advanced glaucoma at the age of 32, on the basis of the appearance of the disks, constricted visual fields, altitudinal in type, and a single tension reading of 30 mm. of mercury. Bilateral cyclodialyses were done, and he was maintained on pilocarpine therapy over twenty-five years, with no further loss of field or visual acuity. At the time of writing, omission of miotics plus provocative tests have resulted in no significant rise in tension. A review of his case indicated that all changes could be explained on the basis of a congenital anomaly.

CASE 3.—*Atrophy of the optic nerve due to syphilis.*

H. R., a white man aged 50, was first seen in the ophthalmic clinic of the Hospital of the University of Pennsylvania in 1939 because of the sensation of a foreign body in his right eye. Corrected visual acuity was 6/6 in each eye, but both disks appeared pale and cupped. Repeated tension readings were in the low 20's. The visual fields showed bilateral inferior nasal arcuate defects (chart 4). Roentgenograms of the skull showed a normal condition. The Wassermann reactions of the blood and spinal fluid were positive, and a diagnosis of tabes dorsalis was later made.

The patient was presented at staff conference, where opinion was divided. Some felt that the cupping represented glaucomatous atrophy, but since it was thought possible for tabetic atrophy to explain the whole picture, glaucoma therapy was withheld. The patient was given a course of treatments with bismuth and neoarsphenamine, in addition to fever therapy (36 hours of fever, with a temperature over 103 F., induced by typhoid bacilli).

The patient has now been followed over ten years. His vision is still 6/6 in each eye. His visual fields have shown no significant change, and the pallor and cupping of his disks remain the same. An increased ocular tension has never been recorded.

Summary.—The diagnosis of glaucoma was suspected in this case because of cupping and typical glaucomatous field defects. Miotics were withheld, and antisyphilitic therapy was given because it was considered that tabetic optic nerve atrophy could produce a similar picture. Since there has been no further loss of visual field or acuity during the past 10 years, a glaucomatous process seems to be excluded.

By way of caution, brief mention should also be made of the opposite situation. Of the newly registered patients in the glaucoma clinic during

the past year, four had originally been sent to the ophthalmic department with the clinical impression of syphilitic optic nerve atrophy because of known syphilis of the central nervous system. All of these patients had definite chronic simple glaucoma.

CASE 4.—*Calcification of the internal carotid arteries.*

H. G., a white man aged 67, was sent in consultation from the neurological service of the Hospital of the University of Pennsylvania because of persistent headaches. Corrected visual acuity was 6/9 in each eye. His optic disks appeared cupped. Repeated fields showed a constant altitudinal defect in the right eye (chart 5). Gonioscopic studies showed open angles. Ocular tensions were under 20 mm. of mercury, and a water provocative test did not alter the pressure. A roentgenogram of his skull showed calcified carotid arteries. In a complete neurological work-up nothing was found to account for the loss of field other than the sclerotic vessels.

PROGNOSIS

The prognosis varies with the etiologic agent. In the rare cases of pseudoglaucoma due to a congenital anomaly the process is stationary. In the few in which the condition is due to tumor the outlook in large part depends on the biologic nature of the tumor. The many papers on sclerosis of the internal carotid arteries as a cause of pseudoglaucoma mention the very slow progression of visual loss. In only one of the hundred-odd cases gathered had the condition progressed to blindness when reported. In addition, pseudoglaucoma of this type occurs in patients well advanced in years, so that the prognosis for maintaining useful vision is relatively good.

TREATMENT

When a puzzling case of "low tension glaucoma" is encountered, an attempt should be made to find the true nature of the disturbance and the proper treatment then instituted.

When the cause is obscure, one might expect to find divergence of opinion in regard to therapy, reflecting the arguments as to whether this condition represents a disease *sui generis* or merely "low tension glaucoma." However, most ophthalmologists advise conservative measures. Even those who feel that low tension glaucoma is a true entity, caused by a lamina which gives way before normal intraocular pressure, comment on the failure of the usual therapeutic measure, medical or surgical, to influence the course of the disease.

Many of these eyes have been subjected to filtering operations, but there seem to be no instances reported in which surgical intervention has favorably influenced the course of the disease. Two authors have advocated surgery to the point of producing hypotony. Elschnig [18] suggested cyclodialysis, but the case of pseudoglaucoma that he cited is one that was followed only a short time; then, "according to the reports of her relatives, the eyesight remained unchanged until the patient's death four years later."

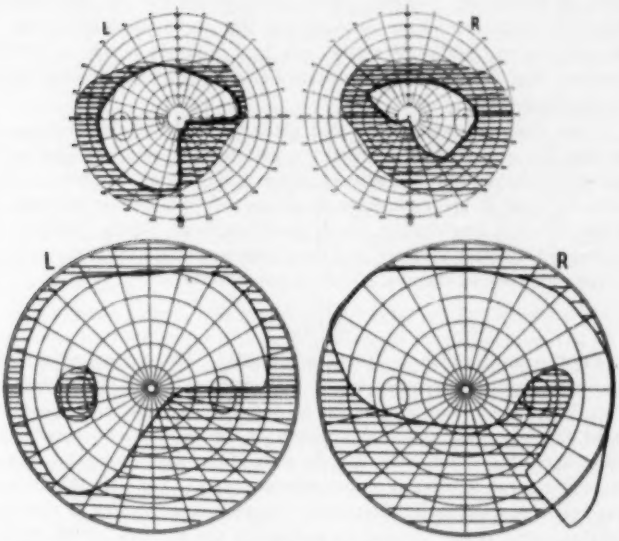

Chart 4 (case 3).—Peripheral (1/330) and central fields (2/1000) in 1938. There is contraction of the peripheral fields, most marked in the lower nasal quadrants. The right eye shows a nerve fiber bundle defect which breaks into the periphery. There has been no further loss of field in 10 year follow-up period.

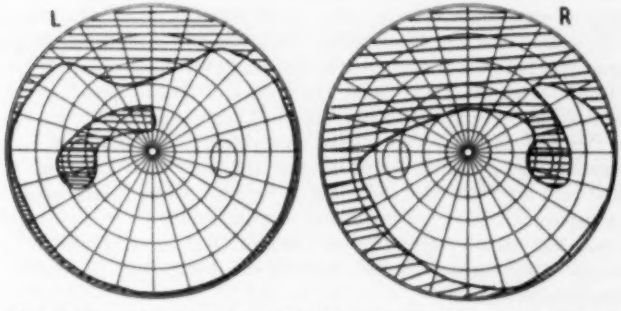

Chart 5 (case 4).—Central fields (2/1000), showing altitudinal and nerve fiber bundle defects, more advanced in the right eye.

Roger Weekers[37] likewise advocated a filtering operation to the point of producing hypotony and stated preference for iridencleisis. However, at the same time, he confessed that operation failed to control the progress of the disease in the only case in which it was performed. Not only that, but after the operation there was decreased visual acuity due to changes in the lens.

Even Sjögren, who stated that glaucoma and pseudoglaucoma are one and the same disease, advised a miotic regimen and was opposed to operative intervention. Actually, from the point of view of therapy, there seems no need to press the issue as to whether this disease is glaucoma or not. Even in true chronic simple glaucoma in an elderly patient, with tension only slightly elevated and deterioration of field slow, the prevailing attitude toward therapy is one of conservatism.[38]

COMMENT

Various terms, such as "pseudoglaucoma," "low tension glaucoma," "glaucoma without hypertension," "soft glaucoma" and "relative glaucoma," have been used to describe a condition characterized by normal ocular tension associated with cupping of the head of the optic nerve and progressive visual field defects compatible with glaucoma. About 100 such cases in which a definite cause was found to explain the findings have been reported in the literature. Congenital anomalies of the disk, syphilitic optic nerve atrophy or tumors in the vicinity of the chiasm were found in perhaps a score of the cases. In the majority, however, the condition was related to sclerosis of the internal carotid arteries. The term "low tension glaucoma" should probably be reserved for the group in which no etiologic factor is found, except perhaps borderline glaucoma, whereas "pseudoglaucoma" might better be applied to the group in which some definite entity can be found to produce the changes in the optic nerve and visual fields which simulate chronic simple glaucoma. This paper adds four additional cases to the relatively small group in which such a cause was found. In these four cases, cupping, pallor of the disks and field defects were present. Each was on a different basis.

The first patient presented the characteristic appearance of slowly progressive glaucomatous field defects, the true cause of which was found only after two years of a miotic regimen, when it was suspected that the cupping was not increasing proportionately. A roentgenogram of the skull then revealed typical changes of a pituitary tumor. The changes in the visual fields have been rendered stationary by irradiation of the pituitary gland.

37. Weekers, R.: Le glaucome incomplet: Contribution à l'étude du glaucome sans hypertension, Ophthalmologica **104**:316, 1942.

38. Dunnington, J. H.: The Surgical Treatment of Primary Glaucoma, Tr. Am. Acad. Ophth. **53**:213, 1949. Scheie, H. G.: The Treatment of Primary Glaucoma by Medical Means, ibid. **53**:186, 1949.

The second patient, though operated on in 1922, in reality had congenital colobomas of the optic nerve. The visual acuity had always been poor, and the fields had not changed during the time of observation. Only one isolated tension reading of 32 mm. of mercury had been obtained.

The third patient had optic nerve atrophy, some cupping of the nerve head and bilateral inferior arcuate defects. His intraocular tension was never found to be elevated. Lumbar puncture showed that he had tabes dorsalis. Although he has been followed for over 10 years, there has been no progress in his visual defects since antisyphilitic treatment.

The fourth patient showed roentgenographic evidence of calcified carotid arteries, which was the only explanation found for the cupping and field defects.

Experience gained with the cases just reported has impressed on us the importance of extremely careful study of all patients who seem to have glaucoma but do not have increase of ocular tension. One must always remember that many lesions of the optic nerve, even in the neighborhood of the chiasm, can produce nerve fiber bundle defects.

It is our impression that patients presenting cupping of the optic nerve, pallor and arcuate field defects, associated with consistently normal ocular tension and negative results in provocative tests, should be carefully studied and, if no explanation is found, their condition should be reevaluated periodically. What proportion of such patients may be found to have "low tension glaucoma" due to a weakened lamina cribrosa or some other mechanism, we are not prepared to say. We do believe, however, that such a diagnosis should be reserved until all other possibilities have been excluded.

SUMMARY

1. The literature covering "pseudoglaucoma," or "low tension glaucoma," is reviewed.

2. The term "pseudoglaucoma" is suggested for that group of cases in which a definite cause is found to explain the optic nerve atrophy and progressive visual field defects. The term "low tension glaucoma" is suggested for that group in which no cause is found or, at most, glaucoma is only suspected. These eyes seem unable to withstand intraocular pressures which fall within what are considered normal limits.

3. Four cases are added to that small group in which an explanation is found. In these cases the etiologic factors were, respectively, (*a*) pituitary tumor, (*b*) congenital colobomas of the optic nerve, (*c*) optic nerve atrophy due to syphilis and (*d*) calcification of the internal carotid arteries.

REPAIR OF ORBITAL DEFORMITIES WITH GLASS WOOL

A Follow-Up Report

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NEW YORK

ABOUT five years ago, because of the large number of orbital deformities associated with war injuries, investigation was initiated of various products which offered possibilities as substitution materials in restoration of fractures of the orbital floor. A preliminary report was made concerning the use of glass wool.[1] Sufficient time has elapsed to permit a more thorough evaluation of this substance and its behavior in orbital tissues.

I have been able to obtain from my own records and from those of surgeons who have sent me résumés of their own cases a total of 19 cases in which glass wool was implanted in the orbit or adjacent structures. In 10 of these, to the best of my knowledge, there have been no untoward effects. Since most of these cases represented war injuries and the patients were treated in Army or Veterans hospitals, follow-up studies have been difficult, and it is quite possible that treatment was not successful in all cases.

In the remaining nine cases the glass wool either was promptly extruded after a preliminary sterile foreign body reaction or remained quietly in place for periods varying from two months to two years after the original operation before extrusion occurred. In several of these cases cultures were taken and revealed no bacterial infection. Removal of the material was performed because of the development of a fistula with persistent serosanguinous discharge. Removal was easily carried out, and there have been no secondary objectionable sequelae.

From this series of patients it would appear that the implantation of glass wool in the orbit is not injurious but that in a high proportion of patients the material is treated as a foreign body and is extruded. Such an occurrence is a probability with any foreign material when the mass is too large to permit easy encapsulation.

It is concluded, therefore, that in its present form the use of glass wool to repair orbital deformities is not satisfactory and that recourse should be made to autogenous tissues, such as bone and cartilage.

From the Institute of Ophthalmology of Presbyterian Hospital and the Department of Ophthalmology of Columbia University College of Physicians and Surgeons, New York, and the United States Veterans Hospital, Bronx, N. Y.

1. DeVoe, A. G.: Repair of Orbital Deformities with Glass Wool, Arch. Ophth. **38**:245-247 (Aug.) 1947.

DETERMINATION OF VOLUME OF THE POSTERIOR CHAMBER OF THE RABBIT'S EYE

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AND
V. EVERETT KINSEY, Ph.D.
BOSTON

A COMPREHENSIVE understanding of aqueous humor dynamics requires knowledge of the rates of transfer of substances of the blood to the posterior chamber, since many constituents of the blood enter this chamber by way of the ciliary body. Studies of this kind are limited not only by the small quantity of fluid available for analysis, but by lack of knowledge of the volume of the fluid in this chamber, since calculation of these rates depends on a knowledge of the volume.

In the present study the volume of the posterior chamber of an eye from a freshly killed rabbit was determined. For this purpose the posterior chamber was arbitrarily defined as that region bounded anteriorly and laterally by the posterior surfaces of the ciliary body and posteriorly by the most anterior extension of the vitreous humor and lens.

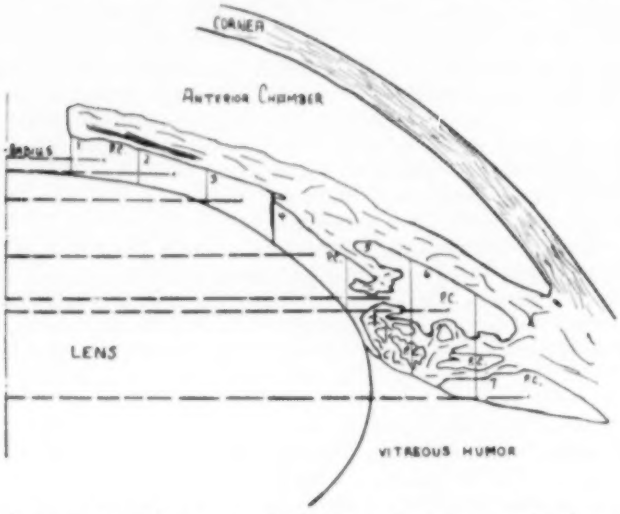
METHOD AND RESULTS

The eye of an adult rabbit was enucleated, fixed in Zenker's solution and stained with hematoxylin and eosin, and six horizontal meridional sections, each 25 microns thick, were made as near to the center of the eye as possible. Drawings of these sections, magnified 40 times, were then made by means of a microprojector. Because of the irregularity of the posterior chamber, it was not possible to compute its volume from a knowledge of the cross sectional area and the inner and outer radiuses of the chamber. To obviate this difficulty, an approximate method was employed in which the cross sections were divided into six or seven blocks, or segments, and the approximate volume of each of these separate segments was then determined from the area and the radius of each segment. The area was measured by means of a planimeter, and the radius was taken as the distance between a line drawn through the center of the lens as a midpoint plane and the center of each segment. The total volume of these segments represents the volume of the posterior chamber. The volumes of six cross sections (a total of 12 sections of the posterior

From the Howe Laboratory of Ophthalmology, Harvard Medical School.

chamber), expressed in microliters, were 41, 56, 55, 55, 59, 58, 58, 61, 54, 81, 48 and 54, the average being 57. Because of the possibility of anterior displacement of the pupillary border of the iris, the calculated volume is probably high.

It is of interest that the volume of the aqueous humor in the posterior chamber of the rabbit's eye is approximately 20 per cent of that in the anterior chamber. Not all of this fluid can be withdrawn for chemical analysis, as one of us (V. E. K.) has repeatedly withdrawn aqueous humor from the posterior chamber by inserting a needle behind the limbus and found that only 5 to 10 microliters could be obtained. Appar-



A cross section of the posterior chamber illustrating segments used in determining the volume of this chamber. The forward displacement of the iris is particularly noticeable in this section.

ently only the aqueous humor from a small segment of the posterior chamber can be withdrawn.

SUMMARY

The volume of the posterior chamber of the adult rabbit eye has been deduced from measurements taken on an eye fixed in Zenker's solution and found to be approximately 57 microliters. This value is approximately 20 per cent of the volume of the anterior chamber.

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Dr. Russell Carpenter, of the Department of Biology, Tufts College, Medford, Mass., made the sections used in this work.

INTRACTABLE POSTOPERATIVE DIPLOPIA

COMMANDER GEORGE L. TABOR JR. (MC), U. S. N.

AS EARLY as 1842 Dieffenbach observed that diplopia might occur suddenly after operation for squint, although it had not been present prior to operation. In recent years there has been much discussion of this dreaded complication among practicing ophthalmologists, but little has been written about it. My interest was stimulated by being so unfortunate as to have a case of intractable postoperative diplopia. It is difficult to determine who suffers more in this experience, the patient or the ophthalmologist. In the collection and correlation of what little information was available on this subject, the literature for the past fifteen years was reviewed, and personal communications were received from seven ophthalmologists who have had wide experience in muscle surgery.

The term intractable postoperative diplopia in this discussion is applied to those cases of double vision which occur after an operation on the extraocular muscles usually in cases of comitant squint with no diplopia prior to operation. It occurs almost exclusively in adults. Guibor [1] has never seen a case in a child, and Morgan,[2] reporting on 800 cases at the Hospital for Sick Children, Toronto, did not mention the complication. Of 2,865 cases of muscle surgery reported in the literature in various series, troublesome postoperative diplopia was observed in 16, approximately one in every 200. All cases occurred in late childhood or adult life.[3] However, analysis of Shure's and Pemberton's

Read before the College of Physicians of Philadelphia, Section of Ophthalmology, Feb. 16, 1950.

The opinions and assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department.

1. Personal communication to the author, 1950.

2. Morgan, A. L.: Surgical Treatment of Strabismus, Canad. M. A. J. **45**:500, 1941.

3. (*a*) Morgan.[2] (*b*) Berens, C.: Surgical Results in 223 Cases of Heterotropia, Am. J. Ophth. **20**:266, 1937. (*c*) Horay, C.: Experience with Advancement of Muscles in 700 Cases, Klin. Monatsbl. f. Augenh. **95**:289, 1935. (*d*) Dunnington, J. H., and Wheeler, M. C.: Operative Results in 211 Cases of Convergent Strabismus, Arch. Ophth. **28**:1 (July) 1942. (*e*) Shure, I. I.: Strabismus in

(*Footnote continued on next page*)

series [e,f] which included adults only, revealed that a total of 120 patients, or one in 12, suffered from postoperative diplopia for considerable periods or permanently. Guyton [g] reported that there had been only six cases at the orthoptic clinic, Johns Hopkins Hospital.

What are the mechanisms at play in these cases of postoperative diplopia, or horror fusionis? Is there a common pattern or several distinct types? Pemberton [f] stated the opinion that anomalous retinal correspondence does not play a role. In fact, he stated that the finding of anomalous projection practically excludes the possibility of permanent postoperative diplopia. However, in persons with true projection, who easily overcome suppression and show no fusion and in whom diplopia can be elicited when correcting prisms are placed before the eyes, there is a great risk of constant diplopia after operation. He cited four cases in which the patients were advised against operation because of the possibility of this complication. Each decided to take the risk, and all had troublesome postoperative diplopia.

Horror fusionis is due to an abnormal position of the eyes and anomalous correspondence, according to Sternberg-Raab.[4] She has found that when diplopia does arise it is usually transitory, because of the awakening of normal correspondence or the return to the preoperative habit of suppression. When the diplopia is permanent, the eyes tend to return to the former squinting position.

Swan [5] reported four cases of alternating esotropia with anomalous retinal correspondence. Suppression of slightly disparate retinal images did not occur, and an annoying diplopia developed after operation. In two patients suppression developed six months after orthoptic exercises were stopped; one could not be followed, and the fourth was still diplopic two years after operation. Swan expressed the belief that the inability to overcome induced aniseikonia and the lack of suppression may possibly explain one type of horror fusionis. He also indicated [1] that indiscriminate surgery on the oblique muscles is a common cause of intractable postoperative diplopia, because of the production of cyclotropia, which

Adults: Analysis of Operative Results in 65 Cases, ibid. **32**:113 (Aug.) 1944. (*f*) Pemberton, E. C.: Prognosis of Post-Operative Diplopia in Adults, Tr. Ophth. Soc. U. Kingdom **63**:370, 1944. (*g*) Berens, C.; Elliott, A. J., and Sobacko, L.: Orthoptic Training and Surgical Correction of Strabismus, Am. J. Ophth. **24**:1418, 1941. (*h*) Kieble, F. A., and Henton, G. H.: The Results of Squint Operations, ibid. **22**:422, 1939. (*i*) Torres Estrada, A.: Surgical Therapy of Concomitant Strabismus: Results in Cases, An. Soc. mex. de oftal. y oto-rino-laring. **12**:17 (July-Sept.) 1937.

4. Sternberg-Raab, A.: On Double Vision with Squint Operations, Brit. J. Ophth. **23**:568, 1939.

5. Swan, K. C.: Some Aspects of Studying Binocular Vision, Am. J. Ophth. **31**:845, 1948.

may become manifest only in other than the primary position of gaze. Cyclotropia may have been a factor in my case, although none could be demonstrated in the primary position.

In Scobee's[1] experience, intractable postoperative diplopia had occurred only in cases of overcorrection of alternating strabismus. It was his belief that the diplopia in these cases was due to the image of the nonfixing eye falling outside what he preferred to call the zone of habitual suppression, anomalous correspondence playing no role in the disturbance.

Hardy[3] noted that intractable diplopia usually occurs in patients who have been operated on in the presence of well established anomalous correspondence, accounting for its predominance in older patients. He expressed the belief that the proper treatment is preventive, i. e., preoperative breaking down of anomalous correspondence.

Romaine,[5] in agreement with Sternberg-Raab,[4] stated that patients with a fixed eccentric retinal area and no fusion at the macula will after surgical correction do one of two things: they will return to the original squint, or their eyes will remain straight and they will complain of diplopia. He further added that persons with true alternating squint operated on after the age of 6 or 7 almost invariably present postoperative problems. This is not my experience.

Krimsky[2] stated the firm opinion that the psychological role requires a thorough investigation, as well as the physiological factors. He expressed interest, furthermore, in the power of suggestion as a means of reducing the patient's concern about his condition. He stated the belief that a study of the relative suppression areas before operation would be most helpful. A large suppression area may speak for the absence of postoperative diplopia.

The most detailed description of horror fusionis has been given by Bielschowsky.[6] In the typical case the angle of squint has been reduced to a few degrees, and the double images are very close but unsteady, both as to distance and as to their relative position, to each other. By means of prisms or a major amblyoscope the images may be made to approach, even overlap, each other, but they never fuse. The image of the nonfixing eye may appear first on one side, and then on the other, of the image of the fixing eye. The reason for this is the avoidance of discomfort when images which cannot be fused are placed before both maculas, i. e., true horror fusionis. He stated the belief that this inability to fuse is not based unconditionally on an anomalous sensorial relationship. Horror fusionis may be due to a congenital or developmental defect of the sensorial apparatus of the occipital lobes. It is an

6. (*a*) Bielschowsky, A.: Congenital and Acquired Deficiencies of Fusion, Am. J. Ophth. **18**:925, 1935; (*b*) Lectures on Motor Anomalies, Hanover, N. H., Dartmouth College Publications, 1940.

atavistic characteristic, in which there is no sensorial correspondence at all between the two eyes. Aniseikonia was also investigated by him and found to have a direct causal relation to horror fusionis in some cases. He noted also that patients with troublesome postoperative diplopia were neurotic and unstable. Grant and Knapp[7] reported a case in which psychopathological factors may have played a role, along with inequality of the retinal images.

Amblyopia bears no particular relation to the development of this distressing complication. Some observers[8] have noted amblyopia in the squinting eye in all their cases. Adrogué and Lagos[8b] stated unequivocally that horror fusionis is due to persistence of abnormal correspondence and that the persistence of the anomalous relation was due to the true amblyopia in their three cases. Bielschowsky and others, however, have found equal vision commoner, the condition occurring more frequently in persons with alternating squint, particularly divergent alternating squint.

Treatment consists first of correcting any refractive errors that may be interfering with fusion, particularly oblique astigmatism. Bielschowsky stated the belief that aniseikonic corrections should also be worn if an incongruence of the retinal images is found. This service, however, is not available to the average ophthalmologist.

A definite and concerted trial of fusional exercises should be made on a major amblyoscope. In several of the most obstinate cases the condition has responded to this treatment, with the eventual development of single binocular vision.[9] Failing this, suppression can be induced by actually teaching the patient to ignore the object by explaining to him the system of blur.[1] It may be necessary to hasten suppression in cases with refractive errors by overcorrecting one eye. This correction is subsequently gradually reduced.[10] Prolonged total occlusion of one eye may be obligatory until suppression is accomplished.[11] Prisms for displacing one image to the peripheral retina have been tried, but with little success.[8a] As a final resort, reoperation to restore the preoperative position can be carried out[12]—a terrible calamity after a patient has endured several muscle operations and has struggled with his double images for a year or more.

7. Grant, H. W., and Knapp, F. N.: Suppression in Antipathy to Single Vision, Tr. Am. Acad. Ophth. **39**:168, 1934.

8. (*a*) Dunnington and Wheeler.[3a] (*b*) Adrogué, E., and Lagos, E. J. J.: Permanent Post-Operative Diplopia in a Case of Strabismus, Semana Med. **2**:804, 1938.

9. Bielschowsky.[6] Shure.[3e] Sternberg-Raab.[4]

10. Bielschowsky.[6a] Romaine.[1]

11. Bielschowsky.[6a] Hardy.[1] Romaine.[1]

12. Bielschowsky.[6] Scobee.[1] Romaine.[1]

REPORT OF A CASE

A white man aged 20 gave a history of convergent strabismus since the age of 2 years, the right eye usually turning in. There was no familial history of squint. He stated that he had become depressed and was embarrassed about his crossed eyes because of the remarks his shipmates were making. He was extremely desirous of surgical correction. No history of diplopia could be elicited.

Examination revealed vision of 20/25 in the right eye and 20/15+ in the left eye.

The eyes showed no organic lesions, and the refractive error was insignificant. A comitant internal squint measuring 20 degrees was demonstrated on the perimeter and by Hirschberg's method. The prism and cover test revealed 45△ of esotropia and 8 to 12△ of left hypertropia for both near and distance. He preferred to fix with his left eye, but fixation could be maintained with the right eye if forced by the examiner.

Worth's four dot test showed a homonymous diplopia, but no diplopia fields could be taken. The after-image test indicated normal retinal correspondence. Fusional studies with foveal targets on the stereo-orthopter and on the telebinocular with prisms disclosed fusion with considerable amplitude and stereopsis on repeated tests. The patient was scheduled for operation with the feeling that the chances of postoperative single binocular vision were excellent.

The left inferior oblique was severed from the globe at its insertion, and the left external rectus was resected and advanced. The immediate postoperative result was 30△ of exotropia. Five weeks later this changed to a convergent squint of 18△ and a right hypertropia of 6 to 8△. Transient diplopia occurred immediately after the operation. The patient was most unhappy with the cosmetic result; so a second operation was performed. The right inferior oblique was severed from the globe, and the right external rectus was resected and advanced. This procedure resulted in a divergent squint of 45△, with a right hypertropia of 0 to 2△. Third grade binocular vision was readily obtained at the angle of the squint. He was kept on convergence exercises for two months, with no improvement in the external deviation. He did not complain of double images, but he could be made aware of a crossed diplopia by the examiner, the false image being faint.

A recession of the right external rectus was then performed. The resulting squint varied from 5△ of esotropia to 10△ of exotropia with a right hypertropic component of 0 to 4△. There was no cyclotropia in the primary position. He complained of persistent and annoying diplopia while conducting his normal daily affairs. However, third grade binocular vision with considerable amplitude was again easily demonstrated on the testing instruments. The after-image test again revealed a normal retinal sensorial relationship. When correcting prisms were placed before the eyes and the patient was told to fixate a light, the left eye held fixation, but the right eye could be seen to stray first in one direction and then in another. As the right eye was wandering, the patient was aware of a change in the relation of the closely approximated double image—typical findings in horror fusionis.

A psychiatric consultation was requested to determine the presence of any psychic disorders that might be contributing to the patient's inability to fuse under ordinary conditions. Under hypnosis he gave evidence of strong feelings of guilt over his having undergone eye surgery without his mother's knowledge or consent and said that he had done a sinful, unfilial thing. Since he was a child ophthalmologists had been recommending operation on his eyes, and this had always been vetoed by the patient's mother, who was stoutly opposed to any and all forms of surgery. One actually obtained the impression that the patient was

rejecting fusion of the images because of his overwhelming sense of guilt. He was then pleased with the cosmetic result and would not hear of occlusion or further surgical measures to restore the eyes to the original convergent position. At the time of discharge, he felt confident about his ability to master the diplopia. However, a year and a half after his last operation he was still aware of his double images.

SUMMARY AND CONCLUSIONS

Four factors in the pathogenesis of intractable postoperative diplopia, or horror fusionis, can be discerned from an analysis of the cases reported in the literature and the experiences of various ophthalmologists. These are not distinct and separate determinants, but one or more factors may be present in any individual case: (1) anomalous retinal correspondence with or without amblyopia; (2) congenital or developmental deficiency of fusion, i. e., complete absence of sensorial correspondence between the two eyes; (3) incongruence of the retinal images (aniseikonia); (4) a psychogenic factor.

The most helpful finding before operation in determining the possibility of postoperative diplopia is the absence of fusion of macular images with considerable unsteadiness of the double images. Either prisms or a haploscopic device may be employed in making this test.

Once diplopia is established, treatment consists of orthoptic exercises, training in suppression, overcorrection or complete occlusion of one eye and, if necessary, restoration of the original squint by additional operation.

A case of intractable postoperative diplopia which is believed to be primarily psychogenic is reported.

DISCUSSION

Dr. William E. Krewson III, Richmond, Va.: Dr. Tabor has covered the literature of his subject thoroughly and has shown considerable initiative in obtaining personal communications from numerous contemporaries in the field of muscle surgery. In fact, he has left little more to be said. Fortunately, the condition is infrequent. While many patients with strabismus experience transient diplopia after operation, few have prolonged postoperative symptoms. I remember one such patient of the late Dr. Luther Peter who actually requested enucleation of one eye for her annoying, intractable diplopia. I am happy to say I have had no such cases myself, and I know of none at the Graduate Hospital. Of course, there is always the possibility that there has been such a patient and that he became thoroughly dissatisfied and went elsewhere. As Dr. Tabor has indicated, the cause is not known, but, in addition to the ophthalmologic picture, a definite psychogenic factor is probably always present. Since it is human not always to admit one's poor results, it is very likely that many such cases are not reported in the literature.

STUDIES IN DEPTH OF THE ANTERIOR CHAMBER OF THE EYE IN PRIMARY GLAUCOMA

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IN COMPARISON with the normal, the anterior chamber in primary glaucoma often appears extremely shallow. This alteration in the depth of the chamber, which is regarded as one of the most characteristic signs of acute glaucoma, has attracted attention from several points of view, particularly with regard to the pathogenesis and etiology of glaucoma.

The shallowness of the anterior chamber in glaucoma has been considered due to a high pressure in the vitreous body. This opinion was held by von Graefe but has not remained unquestioned, since many clinical observations have indicated that a shallow anterior chamber may in itself predispose the patient to glaucoma.

The absence of a generally accepted explanation of the origin and significance of the shallow anterior chamber is due in the main to the complicated state of affairs encountered in investigations of this problem. The considerable experimental data available can be considered applicable to physiological states only under certain conditions, and direct measurements of the depth of the chamber are difficult for several reasons. Thus, the technic of measuring the depth of the chamber has been associated with considerable difficulty, and methods of sufficient accuracy have only recently become available. Moreover, the depth of the chamber in the normal eye displays considerable variations. Only when these are recognized is it possible to judge the significance of the depth of the anterior chamber in glaucoma.

The matter was taken up in the present investigation [1] with the object of making direct measurements of the axial depth of the chamber in glaucomatous eyes and of correlating these measurements with the increase in pressure in glaucoma. The experiments were primarily designed to provide answers to the following questions:

1. Does the depth of the chamber in glaucoma, or in any special form of glaucoma, show a significant difference from that in the normal eye?

1. This paper is a summary in English of a previous work (Rosengren, B.: Studien über die Tiefe der vorderen Augenkammer mit besonderer Hinsicht auf ihr Verhalten beim primären Glaukom, Acta ophth. **8**:99, 1930; **9**:103, 1931).

2. Does any decrease in the depth of the chamber in glaucoma arise as a consequence of the increase in pressure, or is the chamber already shallow before the increase in pressure sets in?

METHOD

In the measurement of the depth of the anterior chamber it would be most correct to determine the distance between the posterior surface of the cornea and the anterior surface of the lens. This, however, presents considerable optical difficulties. In the present investigation this problem has been simplified by measuring the distance between the anterior surface of the cornea and the anterior surface of the lens and using the refractive index of the aqueous humor. It is also necessary to take into account the error arising from variations in the thickness of the cornea. This is unavoidable with the methods available. Hence the depth of the

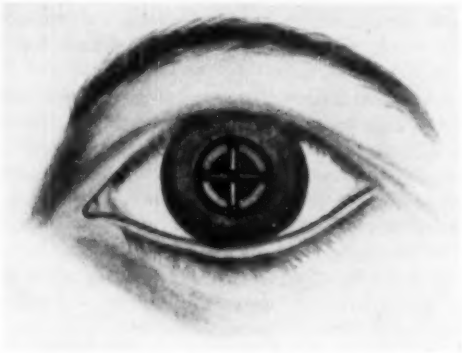


Fig. 1.—Correct setting of the focal lines in measurements with Lindstedt's apparatus (Lindstedt [2]).

chamber will be taken to mean the distance between the anterior surface of the cornea and the anterior surface of the lens.

Technically, there are two main difficulties to overcome. First, settings must be made simultaneously on the anterior surface of the cornea and the anterior surface of the lens, since the movements of the eye between two consecutive settings would involve too considerable an error. Second, it is desirable that measurements be made in the direction of the optical axis of the eye. These two conditions are satisfied only by the apparatus of Lindstedt,[2] worked out at the suggestion of Gullstrand at the eye clinic in Uppsala.

Lindstedt's apparatus is based on the use of an astigmatic pencil of rays with the forward focal line adjusted on the anterior surface of the cornea and the rear focal line on the anterior surface of the lens. The adjustment is performed with the aid of the surface images produced by diffuse reflection at these surfaces, and the

2. Lindstedt, F.: An Instrument for Measuring Depth of Anterior Chamber of the Eye, to Be Used in the Clinic, Inaug. Diss., Uppsala, E. Berling, 1913.

setting of the two lines can be checked simultaneously. The illuminating system consists of a point light source of high intensity reproduced with the aid of Gullstrand's so-called small aspherical ophthalmoscope lens (focal power about +30 D.), together with a planocylindrical dispersing lens (—5 D.) which can be moved in relation to the ophthalmoscope lens. The refractive power in the vertical meridian can thus be altered, and the position of the rear focal line can be varied with respect to that of the forward line. With the aid of a central shutter in front of the ophthalmoscope lens, reflections are eliminated from the observation system. This system consists of a totally reflecting prism mounted centrally on the shutter. This, with the aid of a magnifying glass, permits reading from the side. When the reflected image from the ophthalmoscope lens is adjusted symmetrically in the pupil with the focal lines in the center of the latter, the measurement is carried out in the direction of the normal to the cornea as it passes through the center of the pupil. The direction of the eyes and the accommodation are checked by means of an optometer arrangement placed before the eye not being examined.

When the distance between the cylindrical lens and the ophthalmoscope lens is known, the depth of the chamber may be calculated, and this reading is made directly on the apparatus. There is also a device whereby the value can be corrected for the radius of the cornea. Lindstedt gave the probable error of values obtained by this method as 0.028 mm. From my measurements and statistical calculations, the probable error in an individual measurement in the lower age groups has been found to be 0.03 mm. and that in the higher age groups 0.04 mm.

SPECIAL SOURCES OF ERROR IN MEASUREMENT OF GLAUCOMATOUS EYES

In the measurement of the depth of the chamber in glaucomatous eyes certain special factors enter into the picture. In some cases the measurements were associated with difficulty, due, among other things, to intense pain during acute attacks and to advanced age. While, as a rule, 10 measurements were made on each eye, it was necessary to reduce this number in some cases. Never, however, were the measurements fewer than three. Further sources of error were deficient power of fixation and opacities of the cornea. No measurement is possible when the cornea is very cloudy. Often, however, the opacity varies from time to time. The number of cases in which measurements were quite impracticable was small.

If the opacity is not especially pronounced, the measurement is made with practically as high a degree of accuracy as under normal conditions. This is explained by the fact that in this method use is made of the surface image produced by diffuse reflection. It should be added that even in cases with pronounced opacity of the cornea the measurement may be performed, provided the depth of the chamber has a low value. The image of the anterior surface of the lens then appears relatively sharply through the cloudy cornea, considerably better than in cases with a deep chamber.

The complicating action of miotics has been made the subject of special investigation. It is known that miotics act not only on the pupil but also on the ciliary muscle, producing an accommodation cramp.

Consequently, it might be expected that a reduction in the depth of the chamber would be found to accompany the administration of pilocarpine or physostigmine. Experiments were made with pilocarpine on a total of 30 eyes. Half of these belonged to the 17 to 32 year age group and half to the 45 to 71 year group. After determination of the refraction, the measurement of the chamber depth was carried out, whereupon a 2 per cent solution of pilocarpine hydrochloride was dropped into the eye. The dose was repeated after two minutes. After 30 minutes the refraction was measured and the depth of the chamber was measured anew. The determinations were repeated after 1½ hours.

The results show that in the first group (17 to 32 years) a significant change in refraction to the myopic side was obtained, an average of 3 D., 30 minutes after the administration of pilocarpine. At the same time the mean value for the chamber depth fell in these cases from 3.47 to 3.31 mm. The difference was 0.16 ± 0.033. After 1½ hours the difference was 0.05 ± 0.020 mm.

In the higher age group (45 to 71 years), however, no pronounced changes appeared after 30 minutes. A decrease in refraction could not be established. In some cases, indeed, a slight increase was evident, perhaps associated with miosis. The decrease in depth of the chamber was only 0.02 ± 0.016 mm. After 1½ hours the corresponding value was 0.01 ± 0.011 mm.

For the higher age group, therefore, it is unnecessary to take pilocarpine, the usual medicament in glaucoma, into account as a complicating factor in the measurement of the chamber depth.

MATERIAL

The material employed in this investigation consisted of a number of glaucomatous eyes together with a control series of normal eyes. In the investigation of normal eyes, it was found that the depths of the chambers of the eyes of the same subject were practically identical. This is shown by high coefficient of correlation, which varied somewhat with age, being highest for the lower age groups and somewhat lower at higher ages (0.988 and 0.945). Hence only one eye from each subject was included in the calculations.

The glaucomatous eyes were 104 in number, including 4 with juvenile glaucoma. Fifty-three eyes were from patients with bilateral glaucoma and 51 from patients with unilateral glaucoma. Since the initial purpose of the investigation was to study the relation of the chamber depth to the increase in intraocular pressure in glaucoma, the cases of unilateral glaucoma, of less frequent occurrence, formed a considerable part of the material. In cases of unilateral glaucoma the glaucomatous eye was used in the calculations. In cases of bilateral glaucoma the measurements were made on the eye that permitted the greater accuracy. This was often the eye more altered by glaucoma, since the other could fix with greater certainty in the optometer. As has been mentioned, the number of measurements on a single eye was usually 10, and in no case less than three.

In order that the chamber depth might be studied in different forms of glaucoma, a representative series of cases was necessary. Hence all available uncomplicated

cases were included, although those of unilateral glaucoma were considered preferentially in the first stage of the investigation. It was necessary to exclude a few cases with very cloudy corneas on account of difficulties in measurement. Since only uncomplicated cases were considered, all cases with previous operations were rejected, as well as those in which alterations of some other nature were present. Exceptions were made for cases with moderate nuclear sclerosis and fine cortical cataractous streaks.

The investigation of the material included, as usual, an adequate history, especially reports of earlier acute attacks, cloudy vision and colored rings, observations of any reduction in visual acuity, changes in the field of vision, etc. Visual acuity and refraction were determined in the usual manner, and ophthalmoscopy was employed, in some cases stereoscopically with Gullstrand's ophthalmoscope. All eyes were studied with the corneal microscope and the slit lamp.

In the objective investigation special emphasis was placed on the testing of the visual field, in which a perimeter was employed with an object having an area of 0.25 sq. cm. In cases in which it was especially indicated tests were made with Bjerrum's screen. Tension was measured with the Schiötz tonometer in the usual manner, and the values were reported in accordance with the tonometer scale of 1924.

TABLE 1.—*Mean and Its Standard Error for Normal Eyes of Different Age Groups*

Age, yr.	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-92
Mean	3.57	3.59	3.48	3.37	3.33	3.26	3.16	3.18	3.16	3.15	3.10
Standard error	±0.035	±0.067	±0.050	±0.030	±0.028	±0.034	±0.036	±0.036	±0.029	±0.033	±0.084

Especial attention has been devoted to cases of unilateral glaucoma. Experience has shown that the clinically healthy eye is often affected sooner or later by glaucoma. Such eyes must be regarded as predisposed to glaucoma. In cases in which unilateral glaucoma was diagnosed, the other eye was studied with especial accuracy.

The glaucomatous eyes were classified in accordance with the clinical picture. Such a procedure is clearly associated with great difficulty, and widely different principles have been applied by different authors. This makes it difficult to compare the results of the various surveys of glaucoma. The value of such a classification is thus questionable, especially as the terminology is not standardized. The following classification has been followed in the present account:

Glaucoma irritativum acutum is the term applied to all cases with typical acute attacks and to those with typical prodromal attacks.

Glaucoma simplex covers cases without acute exacerbations. In some of these cases, however, the observation of colored rings was recorded.

Glaucoma irritativum chronicum is the designation used in cases with persistent congestion or opacity of the cornea when these symptoms were of a lasting character and the history showed glaucomatous alterations of long standing.

The control material consisted of normal eyes, 810 in number. The first series comprised 310 eyes, of persons between 25 and 74 years of age. In all these subjects both eyes were measured. Ten determinations were made on each eye, and the mean and its standard error were noted. The coefficient of correlation between the values for the right eye and those for the left eye was calculated for each five year age group. For these 310 subjects the readings for the right eye were used in the calculations. In order to enlarge the control material, the depth

of the chamber was subsequently measured on an additional 500 eyes, of persons from 40 to 88 years of age. Here, however, the procedure was somewhat simplified, in that only three measurements were carried out on each eye. Nor was the radius of the cornea determined in each case; but the apparatus was set at a standard value of 7.8 mm., which involved an inconsiderable error (< 0.05 mm.). A further simplification was involved by dispensing with the optometer, the eye being set on a fixation mark at a distance of 1 meter. In each five year period for age groups from 25 to 40 years 30 eyes were studied, and for each corresponding interval of age groups from 40 years on 50 eyes were studied, the last group including patients over 75 years of age. In this section of the material of 500 cases the right eye was measured as a rule, but the left eye was employed when the other displayed alterations.

DOES DEPTH OF CHAMBER IN THE GLAUCOMATOUS EYE DIFFER FROM THAT IN THE NORMAL EYE?

An answer to this question is rendered difficult by the very appreciable variations in the depth of the chamber in normal eyes, some of them individual in character and some determined by age and refraction. It is hence impossible from a comparison of individual glaucomatous eyes and of individual healthy eyes to arrive at any conclusion regarding alterations in the depth of the chamber in glaucoma. This is possible only if the normal variations can be eliminated. I shall therefore first consider how far and under what conditions this may be achieved.

Variation of Depth of Chamber with Refraction.—This factor, or, more precisely, the variation of the refraction with the depth of the chamber, is without influence on the present problem. If the material is chosen at random and if care is taken to avoid overrepresentation of categories in which the chamber depth differs systematically from that of the normal eye, e. g., school myopia, then the circumstance that a small chamber depth is usually accompanied with hypermetropia and a large chamber depth with myopia is in itself of no importance. Only if the material is classified with respect to refraction will the relation of chamber depth to refraction become a complicating factor. In such a case it is essential to take into account, among other factors, the relative distributions of the various states of refraction in the different groups.

Reduction in Depth of Chamber with Increasing Age.—This is, on the other hand, a complicating factor, making it impossible to compare eyes from different age groups. This factor can, however, be eliminated. A means to this end, which is immediately obvious, is to divide the material into small age groups and to compare healthy and glaucomatous eyes from the same group. However, the numbers available for comparison are then small. An alternative procedure, if the variation of the depth of the chamber with age is known, is to eliminate this factor by reducing the chamber depths for the various age groups by calculated corrections, so that all the eyes may be regarded as belonging to one and the same age group. The latter procedure has the advantage that it is unnecessary to divide the material.

Individual Variations in Depth of Chamber.—These variations are very great, and the material to be compared shows a considerable scatter.

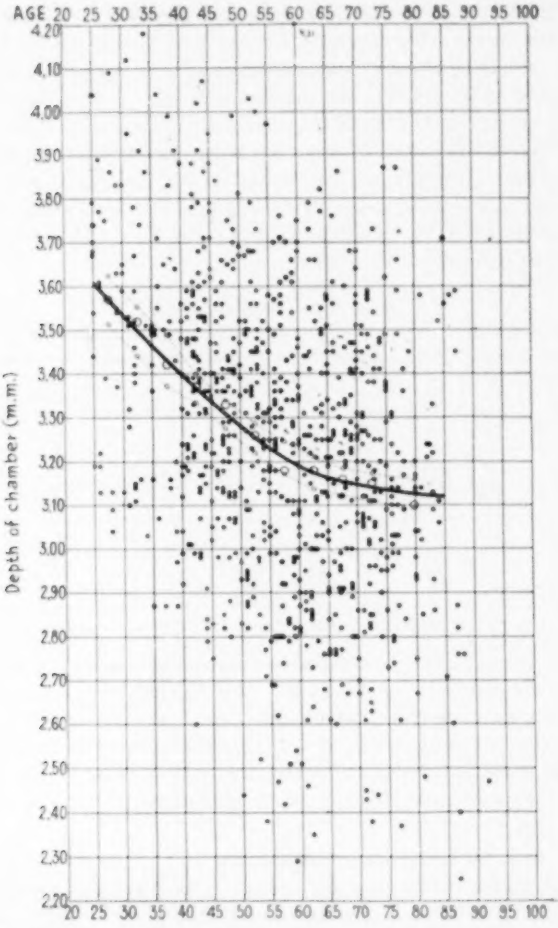


Fig. 2.—Depth of the chamber in normal eyes (Rosengren,[1] page 135).

The requisite for comparing two groups with a certain scatter is that each group contain a sufficient number to provide a well established mean value. Then, by comparison of the means, it is possible to determine whether the difference is significant or fortuitous.

Analysis of Material.—The material to be compared in the present case consisted of the 810 normal eyes and the 100 glaucomatous eyes (104 glaucomatous eyes minus the 4 eyes with juvenile glaucoma).

The depths of the chambers of the normal eyes are shown in figure 2. The means were calculated for five year periods (table 1), and with the aid of these values a fitted curve was drawn, showing the reduction in the depth of the chamber with age. Two curves (dotted lines) on either side of the fitted curve indicate the standard error. On the basis of this material, corrections were calculated for the different age groups (table 2), so that the values for these groups could be adjusted to a chamber depth corresponding to that for 70 years of age. The mean value for the chamber depth was then 3.15 mm., with a standard error of ± 0.011 mm.

TABLE 2.—*Correction for Age*

Age	Correction	Age	Correction	Age	Correction	Age	Correction	Age	Correction
23	−0.48	37	−0.28	51	−0.12	65	−0.01	79	+0.02
24	−0.47	38	−0.27	52	−0.11	66	−0.01	80	+0.03
25	−0.46	39	−0.26	53	−0.10	67	−0.01	81	+0.03
26	−0.44	40	−0.25	54	−0.09	68	−0.00	82	+0.04
27	−0.43	41	−0.24	55	−0.08	69	−0.00	83	+0.05
28	−0.41	42	−0.22	56	−0.07	70	−0.00	84	+0.05
29	−0.40	43	−0.21	57	−0.06	71	−0.00	85	+0.06
30	−0.38	44	−0.20	58	−0.05	72	−0.00	86	+0.07
31	−0.37	45	−0.19	59	−0.04	73	+0.01	87	+0.08
32	−0.35	46	−0.18	60	−0.04	74	+0.01	88	+0.08
33	−0.34	47	−0.16	61	−0.03	75	+0.02	89	+0.09
34	−0.33	48	−0.15	62	−0.03	76	+0.02	90	+0.10
35	−0.31	49	−0.14	63	−0.02	77	+0.02	91	+0.10
36	−0.30	50	−0.13	64	−0.02	78	+0.02	92	+0.11

The values for the glaucomatous eyes are given in figure 3. As in the case of the normal eyes, these were divided into five year groups. With the use of the correction factor for age, values were obtained which made it possible to regard all the cases of glaucoma as corresponding to one and the same age group (70 years). After this reduction, the mean value for the chamber depth of all the glaucomatous eyes was 2.93 ± 0.050 mm.

If the value for the glaucomatous eyes, 2.93 ± 0.050 mm., is compared with the normal chamber depth for the corresponding age (70 years), 3.15 ± 0.011 mm., a difference of 0.22 ± 0.051 mm. is found. This difference is more than three times the standard error and may be regarded as significant. Hence it may be concluded that the glaucomatous material as a whole showed a smaller average chamber depth than did the normal material.

While it may at first be concluded that all cases of glaucoma show this difference, the result might also be due to differences shown only by certain cases. It is consequently of interest to compare the values for the different types of glaucoma. For glaucoma irritativum acutum the

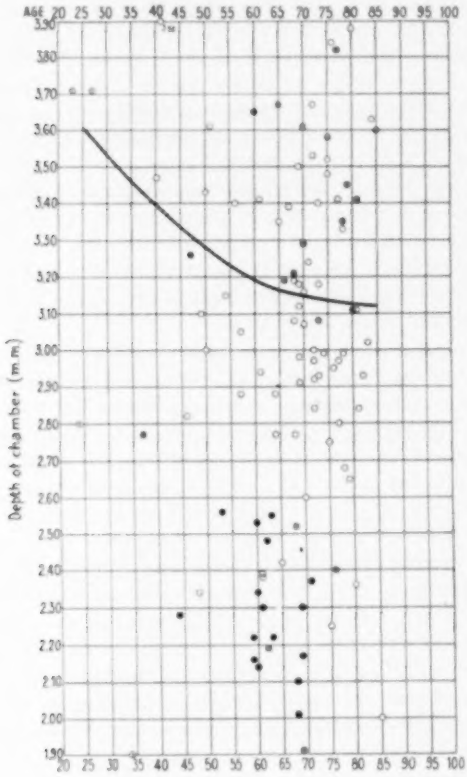


FIG. 3.—Depth of the chamber in glaucomatous eyes, with the curve for the normal chamber depth superimposed. In this graph, values for glaucoma irritativum acutum are shown by solid circles; values for glaucoma simplex, by clear circles; values for glaucoma irritativum chronicum, by circles with cross, and values for glaucoma juvenilis, by circles with dot (Rosengren,[1] page 137).

mean value in the present material is 2.38 ± 0.093 mm.; for glaucoma simplex, 3.04 ± 0.050 mm., and for glaucoma irritativum chronicum, 3.11 ± 0.134 mm. Hence, for glaucoma irritativum acutum the differ-

ence is highly pronounced, being about eight times the standard error, whereas for glaucoma irritativum chronicum and glaucoma simplex no difference is detectable. It consequently appears that a shallow anterior chamber is not associated with the entire series of glaucomatous eyes but only with those with acute irritative glaucoma.

When the above values are considered, however, it must be borne in mind that they are related to the system of classification employed. As has previously been emphasized, the boundaries between different forms of glaucoma are by no means clearly defined, and other authors might perhaps have classified the material in a different manner, with a corresponding effect on the values. If one goes so far as have certain authors, e. g., Elschnig,[3] and places all cases with external irritation in a single group, then with the present material one obtains for this group a mean value of 2.75 mm., which shows a difference from that for simple glaucoma by no means so well established. In view of the element of uncertainty encountered in the classification of any glaucoma material, it is somewhat dangerous to analyze this material on the basis of clinical differences noted in the usual manner.

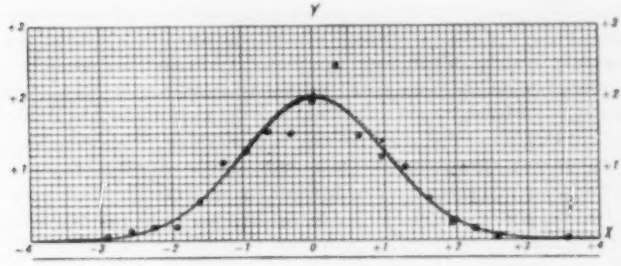
For this and other reasons it is of interest to compare the frequencies of different depths of chamber in normal and in glaucomatous eyes. If the chamber depth in all cases of glaucoma were less than normal, it would be expected that the frequency curve for glaucoma would have the same appearance as the curve for normal eyes but would be displaced with repect to the latter. If, on the other hand, a shallow anterior chamber occured in only a certain part of the material, this would be reflected in a corresponding change in the appearance of the curve.

When the present material of normal eyes, 810 in number, is investigated with respect to the frequencies of different chamber depths and when the values are corrected in the manner described above, that is, for the reduction in chamber depth with increasing age, and are grouped in intervals of 0.10 mm., the curve shown in figure 4 is obtained. This is symmetrical and practically coincides with the gauss curve, having an axis of symmetry corresponding approximately to the average depth of chamber, 3.15 mm.

If a frequency curve for the glaucomatous eyes is constructed in the same manner after reduction of the chamber depth with respect to age and with the same group interval, this curve is found to have a quite different appearance. It differs from the curve for normal eyes in having two maxima, one corresponding to that of the curve for normal eyes and

3. Elschnig, A.: Glaukom, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Springer-Verlag, 1928, vol. 11, p. 873.

the other occurring at a chamber depth of 2.30 mm. (fig. 5). That this difference is not fortuitous can be shown by calculating the number of cases in a series of 100 normal eyes that would have lain beyond twice the standard deviation (σ). Only 2.3 per cent would have lain at values below 2 σ, corresponding to a chamber depth of 2.55 mm. In the present series of 100 glaucomatous eyes, however, 28 have a depth of chamber less than 2.55 mm., about 12 times the number to be expected.



N = 810	F (x) = 52 Y.
M = 3,1407	S = + 0,0489 ± 0,043
σ = 0,3098	E = — 0.0099 ± 0,022

FIG. 4.—Frequency curve for the depth of the chamber of the normal eyes, calculated according to Charlier (Rosengren,[1] page 140).

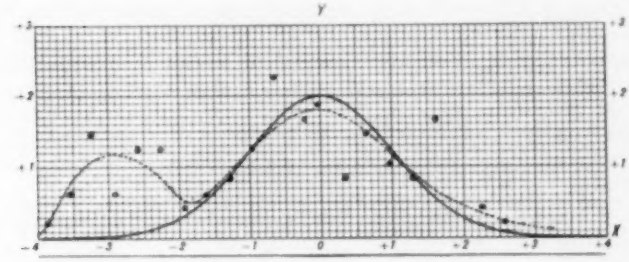


FIG. 5.—Fitted curve for the depth of the chamber of glaucomatous eyes (Rosengren,[1] page 141).

It therefore follows that the small depth of chamber is not found uniformly throughout the material. The greater part of the material displays a distribution about a maximum of approximately about 3.15 mm., nearly the normal value. The difference between the frequency curve for glaucoma and the curve for normal eyes consists in an extra maximum at a chamber depth 2.30 mm., to which there is no counterpart

in the curve for normal eyes.[4] Since, apart from this maximum, the curves are largely coincident, the shallower chamber in glaucoma must be due, at least for the greater part, to a considerable number of cases with a very shallow chamber.

IS THE SHALLOWNESS OF THE ANTERIOR CHAMBER IN GLAUCOMA CAUSED BY THE INCREASE IN INTRAOCULAR PRESSURE?

The shallowness of the anterior chamber in glaucoma may be explained in two ways. It may be assumed, on the one hand, that the depth of the chamber is affected by the glaucomatous process (the increase in intraocular pressure) and hence is in some manner reduced. On the other hand, there is the possibility that the shallow anterior chamber provides favorable conditions for the appearance of glaucoma and that, because of this, a remarkably large number of cases of shallow chambers occur among glaucomatous eyes.

A decision in this matter would be achieved most reliably by measurement of the depth of the chamber in one and the same eye before and after the appearance of glaucoma. This opportunity, naturally, offers itself very rarely—in the present material in only one instance.

It would also be of interest to measure the depth of the chamber during and after an attack of increased intraocular pressure. If the increase in pressure were the determining factor, this should then be discernable. In certain instances during the present investigation it has been possible to perform such measurements.

Essentially, however, it has been necessary to reach a decision by the study of cases of unilateral glaucoma. It is assumed that the healthy eye shows the depth of chamber prevailing under normal conditions, whereas the glaucomatous eye displays a depth of chamber influenced by the glaucomatous process. Since under normal conditions there is scarcely any difference between the depth of the chamber in the two eyes of the same subject, the requirements are fulfilled for a comparison of this kind.

Measurements on the Same Eye Before and After Commencement of Glaucomatous Increase in Pressure.—In the present material it was possible in one case to measure the depth of the chamber on an occasion when the eye showed no sign of glaucoma, before glaucoma simplex developed in the same eye. When the depth of the chamber was first

4. The concept of different groups in a glaucoma series with different depths of chamber, has previously been discussed by Raeder (Raeder, J. G.: Untersuchungen über die Lage und Dicke der Linse im menschlichen Auge bei physiologischen und pathologischen Zuständen, nach einer neuen Methode gemessen: II. Die Lage der Linse bei glaukomatösen Zuständen, Arch. f. Ophth. **112**:29, 1923). This author did not, however, make an accurate comparison of the frequency curve for normal eyes and that for a representative series of glaucomatous eyes.

measured, glaucoma had already been diagnosed in the other eye. At this time the depth of the chamber in the healthy eye was 2.41 mm. One year later, when well developed glaucoma simplex was present in this eye also, the depth of the chamber was 2.37 mm. The small difference falls within the limits of the accuracy of measurement.

Measurements on the Same Eye During and After an Acute Attack.—In four cases it was possible to measure the depth of chamber during and after an acute attack. In the first three cases, of typical glaucoma irritativum acutum, there was no detectable difference between the depth of the chamber during and after the attack. The fourth case was of special interest. The eye in question had not, so far as it was possible to judge, had any previous attack of glaucomatous increase in pressure. The acute attack came about as a result of the patient's accidentally dropping atropine into the eye, and it was relieved with miotics after several hours. There were no subsequent signs of glaucoma. The depth of the chamber showed no detectable difference during and after the attack.

Measurements in Cases of Unilateral Glaucoma.—A comparison of the healthy and the glaucomatous eye in cases of unilateral glaucoma is based on the fact that the depths of the chambers under normal conditions are practically identical in the same person. Considerable differences therefore indicate that conditions are abnormal. Small differences, apart from errors in measurement, may occur normally, so that any conclusions founded on individual cases will be subject to some uncertainty. If, however, a relatively large material is available, such fortuitous differences will become unimportant, and any difference obtained between the mean values must indicate a systematic change in the chamber depth. Furthermore, a possible effect on the depth of the chamber may be studied by calculating the coefficients of correlation between the two eyes for persons in good health and for patients with unilateral glaucoma.

The total glaucoma material, which showed a depth of chamber significantly different from that of normal eyes, contained 48 cases of unilateral glaucoma. The mean value for healthy eyes was 2.90 mm., and that for affected eyes, 2.90 mm. There is hence no difference. If the correlation between the healthy and the glaucomatous eyes is calculated, a coefficient of correlation of 0.983 is obtained, this being about the normal value.

If, in this series of cases of unilateral glaucoma, the mean values are calculated for the cases of glaucoma simplex, glaucoma irritativum chronicum and glaucoma irritativum acutum, it is found that cases of glaucoma simplex show a mean of 3.16 mm for the healthy eye and 3.13 mm. for the affected eye. The correlation is high (0.972). Corresponding figures for cases of glaucoma irritativum chronicum are

3.02 and 3.05 mm., and the correlation coefficient is 0.972. Most interesting is the case of glaucoma irritativum acutum. As has been mentioned, this form of glaucoma is especially attended by a shallow chamber. In 12 cases of unilateral glaucoma irritativum acutum, the mean value for the healthy eyes is 2.31 mm. and that for the glaucomatous eyes 2.30 mm. There is no significant difference, the coefficient of correlation being 0.926.

When one selects the cases that do not correspond to the normal distribution, one finds that 19 cases of unilateral glaucoma belong to this group. The mean value for the healthy eyes is 2.33 mm. and that for the glaucomatous eyes 2.32 mm., with the coefficient of correlation 0.907.

With the aid of these data, it is possible to answer the question posed at the beginning of this section. The depth of the chamber is not affected by the increase of intraocular pressure in glaucoma. The demonstrable difference in depth of chamber between healthy and glaucomatous eyes must already have been present before the setting in of the glaucomatous process and must be independent of the latter.

FURTHER CONCLUSIONS REGARDING THE RELATION OF DEPTH OF CHAMBER TO GLAUCOMATOUS INCREASE IN PRESSURE

It may be taken as established that the depth of chamber in glaucomatous eyes differs from that in normal eyes largely in that among the glaucomatous eyes there is a group with very shallow chambers, which has no counterpart in normal eyes of the same size. On the basis of this fact and the observation that the depth of the chamber is not reduced as a consequence of the glaucomatous increase in intraocular pressure but that the chamber is already shallow before this increase sets in, certain conclusions may be drawn.

It cannot be the result of chance that such a large number of eyes with an initially small depth of chamber are present in a glaucoma material. A normal material with the same number of shallow chambers would necessarily be many times as large—to judge from the available data, at least 12 times as large and, considering the relatively high distribution of cases with extraordinarily shallow chambers, probably even more.

If the cases of glaucoma to be evaluated are regarded as deriving from a group of a very much larger number of normal eyes, the distribution characterizing the glaucoma group (containing cases with very shallow chambers) can be obtained only under certain conditions. It can be obtained only if the eyes in the normal group with very shallow chambers become glaucomatous to a large extent, while eyes with a more ordinary depth of chamber are affected to a negligible extent. The distribution typical of a glaucoma material thus necessitates that eyes with a shallow anterior chamber be, for some reason, affected more

readily by glaucoma than are other eyes. A shallow anterior chamber must predispose the eye to glaucoma.

The question now arises as to how the shallow anterior chamber gives rise to glaucoma. The present measurements of the depth of the chamber obviously cannot provide an answer to this question in all its implications. There is, however, a possibility of studying the relation by a consideration of the clinical picture in the cases in which glaucoma has developed as a consequence of the shallow chambers. These may be distinguished from the other cases of glaucoma with the aid of the frequency curve for glaucomatous eyes (fig. 5).

In the present glaucoma material, 28 eyes (28 per cent) had a depth of chamber below 2.55 mm., whereas in a normal material of the same magnitude only 2.3 per cent would have had such shallow chambers. When the clinical pictures of the 28 patients are studied, the remarkable circumstance comes to light that the majority could be shown, either on reception at the clinic or by the history, to have had acute attacks. In 18 cases acute attacks, and in 5 cases colored rings, were mentioned. In only 5 cases could no acute symptoms be demonstrated. It should be noted, however, that only incomplete histories could be obtained from some patients and that several of these had been treated for long periods with pilocarpine. A striking predisposition to acute attacks is thus characteristic of eyes with a shallow anterior chamber. Whether, as is generally supposed (Seidel[5]; Serr[6]), blocking of the angle of the iris, when the pupil is dilated, is the decisive factor cannot be decided on the basis of the present investigation. The predisposition to glaucoma caused by a shallow anterior chamber, considered together with rapid, but transient, increases in pressure, suggest, however, a circulatory obstacle of a crude, mechanical nature.

A further characteristic feature of the clinical picture for eyes with a shallow anterior chamber is that in certain cases a state of glaucoma simplex developed. Sometimes this appeared in an uncomplicated form (3 cases) or with only the observation of colored rings (4 cases). In other instances, however, it may be suspected that it was a stage following earlier acute attacks (4 cases). A shallow anterior chamber must thus also predispose the eye to glaucomatous increases in pressure of a chronic nature.

It may be asked whether the earlier acute attacks had a causal significance (synechia formation) or whether glaucoma simplex developed

5. Seidel, E.: Weitere experimentelle Untersuchungen über die Quelle und den Verlauf der intraokularen Saftströmung, Arch. f. Ophth. **102**:415, 1920; Zur Methodik der klinischen Glaukomforschung, ibid. **119**:15, 1927-1928.

6. Serr, H.: Augendruckkurven, Ber. d. deutsch. ophth. Gesellsch. **46**:398, 1927.

independently. Even if the latter possibility appears the more likely, the question must at present be left unanswered.

It is impossible, with the present material, to make a closer analysis of the connection between the depth of chamber and the glaucomatous increase in intraocular pressure. The thesis maintained here, that an initially shallow anterior chamber is a cause of glaucoma, might certainly give rise to a discussion of certain related problems. Further study of these questions will, however, require another material, investigated by another method.

CONCLUSIONS

1. The depth of the anterior chamber in glaucomatous eyes is, on the average, less than that in normal eyes. This smaller depth is not shown, however, by the whole series. It may be explained by the fact that the glaucoma series contains a group of cases with a very shallow chamber, which has no counterpart in a series of normal eyes of the same magnitude.

2. The shallow anterior chamber in glaucomatous eyes is not a consequence of the increase in intraocular pressure. The difference in depth of the chamber demonstrable between normal and glaucomatous eyes exists before the pressure increases and has been shown to be independent of this increase.

3. The shallowness of the anterior chamber in glaucoma is explained by supposing that a shallow chamber predisposes the eye to glaucoma.

4. Eyes which become subject to glaucoma as a consequence of a shallow anterior chamber are characterized by the occurrence of acute attacks in the majority of cases. In certain instances, however, the glaucoma takes the form of uncomplicated glaucoma simplex.

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RETINAL CAPILLARY LESIONS IN MALIGNANT HYPERTENSION

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IN RECENT years attention has been focused on the study of the retinal capillaries in systemic vascular disease, since there is little question that the dynamic physiology of the retina is dependent on the integrity of the capillary circulation. In diabetes, for example, capillary microaneurysms have been described by all workers in this subject as the most characteristic retinal capillary lesion in this disease. In explanation of retinal hemorrhages and so-called exudates, such local vascular disturbances as capillary and precapillary stasis and dilatation were suggested by Elwyn [1] some years before retinal capillary lesions were observed histologically. Anatomically, Michaelson and Campbell [2] in 1940 pointed out that the deep retinal capillary plexus is a more closely knit meshwork than the superficial and that venous stasis occurs mostly in these deeper capillaries, where exudates and hemorrhages are more numerous.

For some years it has been recognized that in the study of the retinal circulation cross sections of the retina afford an unsatisfactory view of the capillaries, and, in fact, of the smaller arterioles and venules as well. These difficulties have been surmounted in large measure by the preparation and study of the entire thickness of retina. By this means the retina is mounted flat on slides, and the thinness and relative transparency of the tissue permits a satisfactory study of the deeper retinal circulation. Two distinct capillary plexuses are thus brought into view, and the

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Read before the New York Academy of Medicine, Section of Ophthalmology, March 20, 1950.

1. Elwyn, H.: Diseases of the Retina, Philadelphia, The Blakiston Company, 1946, p. 4.

2. Michaelson, I. C., and Campbell, A. C. P.: Anatomy of the Finer Retinal Vessels and Some Observations on Their Significance in Certain Retinal Diseases, Tr. Ophth. Soc. U. Kingdom **60**:1, 1940.

communications of one with the other are readily traced by adjustment of the focusing mechanism of the microscope.

Ballantyne and Lowenstein [3] in 1944 first used glycerin-mounted specimens of the retina in bulk to study the retinal vessels in various diseases affecting the retinal circulation, particularly the retinal veins. In some of these bulk specimens they injected the retinal vessels with a gelatin-blood mixture and stained the vessels with benzidine. New-formed capillary loops were thus demonstrated, and microaneurysms were seen on gross examination of the specimens. As far as diabetes was concerned, the retinal veins were found to bear the brunt of the disease, and the histological changes noted in them conformed generally to those found ophthalmoscopically, namely, (*a*) dilatation or overfilling, (*b*) variation in caliber, (*c*) sheathing, (*d*) microaneurysms, which may be attached to the finest venules or dilated capillaries, and (*e*) at a later stage, new-formed vessels in the retina or optic disk.

Ballantyne [4] pointed to the occurrence of minute globular aneurysms in the macula as probably the earliest unequivocal sign of diabetes. He described them as "mulberry-like" bodies, composed of a compact mass of erythrocytes enclosed in a membrane of varying thickness. They occur in the course of the capillaries which join the superficial and deep capillary plexuses, usually at the level of the inner nuclear layer. According to this author, they may occur in hypertension, but here they are not confined within the limits of the central area of the retina and are always associated with obvious vascular disease. Ballantyne pointed out that the earliest visible change in diabetes is in the capillaries closest the venules; and from this disturbance arise a whole series of retinal changes recognizable as diabetic retinopathy. In hypertensive vascular disease the earliest involvement is in the precapillaries and arterioles, and from it develop the visible vascular changes, hemorrhages and exudates typical of hypertensive retinopathy.

In 1948, Jonas Friedenwald [5] made perhaps the most significant contribution to these studies by applying a modification of the technic of Hotchkiss [6] and McManus,[7] the so-called periodic acid–Schiff reagent

3. Ballantyne, A. J., and Lowenstein, A.: Retinal Microaneurysms and Punctate Hemorrhages, Brit. J. Ophth. **28**:593, 1944.

4. Ballantyne, A. J.: Retinal Changes Associated with Diabetes and with Hypertension: Comparison and Contrast, Arch. Ophth. **33**:97 (Feb.) 1945.

5. Friedenwald, J.: A New Approach to Some Problems in Retinal Vascular Disease, Am. J. Ophth. **32**:487, 1949.

6. Hotchkiss, R. D.: A Microchemical Reaction Resulting in Staining of Polysaccharide Structures in Fixed Tissue Preparations, Arch. Biochem. **16**:131, 1948.

7. McManus, J. F. A.: Histological Demonstration of Mucin After Periodic Acid, Nature, London, **158**:202, 1946; Histologic and Histochemical Uses of Periodic Acid, Stain Technol. **23**:99, 1948.

stain, to bulk sections of the retina. With this stain, the endothelium of the whole vascular tree is surrounded by a brilliantly stained basement membrane. In infants up to 2 years of age this basement membrane of the retinal vessels is thinner and less visible, hence apparently poorly developed. In specimens of diabetic retinas thus stained the capillary aneurysms are strikingly clear. In some capillaries tiny knuckles can be seen in the walls, possibly representing the first stage in the aneurysm formation. Friedenwald stated that similar capillary aneurysms are occasionally seen in cases of retinal vascular disease in nondiabetic patients but they are rare, and when they occur not more than two or three are observed in a whole retina. He concluded that the capillary aneurysms of diabetic retinopathy quite characteristically distinguish this disease from the retinopathy of arteriosclerosis or of malignant hypertensive vascular disease.

Ashton [8] in 1949 studied the retina in 28 eyes of diabetic patients, using Friedenwald's modification of the periodic acid–Schiff's reagent stain, and stated that the microaneurysms are true aneurysms. These lesions were not seen, with the same staining technic, in the cerebral vessels, pericardium, pleura, meninges, renal capsule, liver or bladder of diabetics, irrespective of whether diabetic retinopathy was present or not.

Essentially, the periodic acid technic consists in the application of periodic acid and so-called Schiff's reagent to bulk sections of retina. The chemical rationale for the use of periodic acid is based on the fact that, when acting on a carbohydrate and some of the alpha-amino alcohols, periodic acid produces an aldehyde. When Schiff's reagent, or leuko-basic-fuchsin, is added to this aldehyde, the reagent takes on a red or violet color. This property has been applied to histochemical technics. McManus has found that renal basement membranes, capillary walls, mucin, glycogen, the hyalin of arteriosclerosis, amyloid and the fibrin of venous thrombi are strongly colored with the periodic acid routine. Ordinary connective tissue stains little, if at all; the tunica elastica is not stained, and there is no nuclear coloring.

The periodic acid technic has proved to be an excellent histological stain. However, McManus [9] has pointed out recently that histochemical conclusions are difficult to reach, despite the demonstration of aldehyde in tissue sections by Schiff's reagent after the action of periodic acid. Lison [10] has shown that a great variety of materials other than aldehydes

8. Ashton, N.: Vascular Changes in Diabetes with Particular Reference to the Retinal Vessels: Preliminary Report, Brit. J. Ophth. **33**:407, 1949.

9. McManus, J. F. A.: Periodic Acid Routine Applied to the Kidney, Am. J. Path. **24**:673, 1948.

10. Lison, L.: Histochimie animale: méthodes et problèmes, Gauthier-Villars, Paris, 1936.

will color Schiff's reagent; many substances in tissues contain one or both of the linkages from which periodic acid can produce aldehyde. In view of these facts, some of which were published subsequent to Friedenwald's paper, in 1948, one or two of this author's statements regarding the specificity of periodic acid as a histochemical stain should perhaps be clarified. Suffice it to say that the periodic acid–Schiff reagent stain is a striking and convenient method, far superior to any

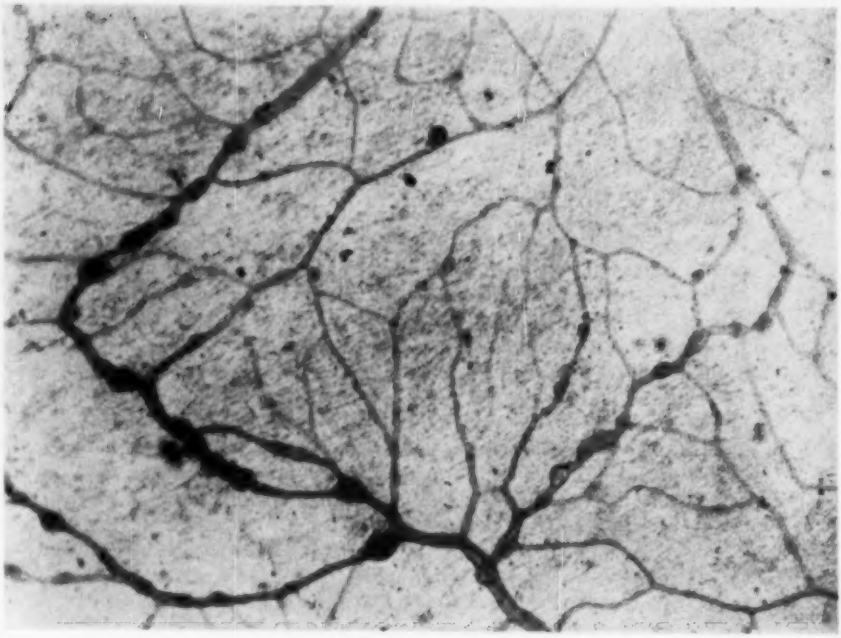

Fig. 1.—Capillary dilatation and sacculation in diabetes; × 30.

previous method for staining capillaries, but that the last word on the histochemical properties of the lesions demonstrated must await further investigation.

The present report is based on the study of bulk preparations of the retinas of 53 eyes. These had been accumulated over a period of about twenty years and had been first studied in cross section. The retina was secured from the preserved paraffin block by melting away the paraffin and dissecting the retina from the globe. Staining was done by the periodic acid–Schiff reagent technic according to the method outlined by

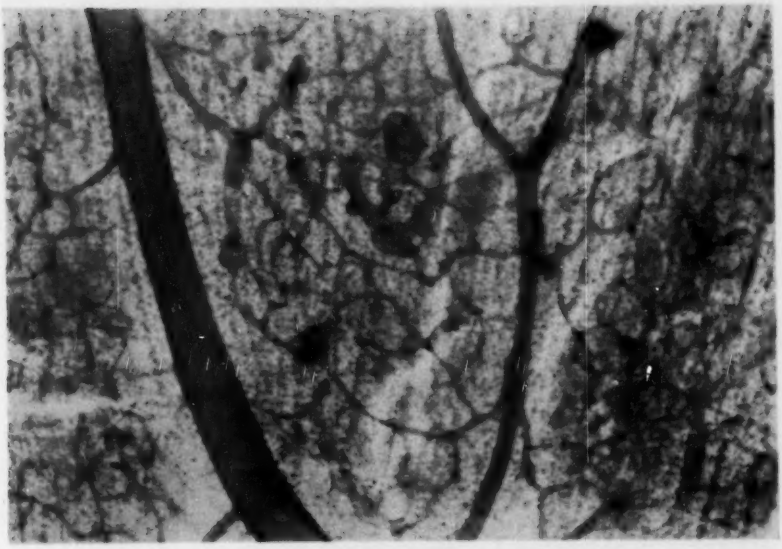

FIG. 2.—Capillary dilatation and microaneurysms in diabetes. The two large vessels are arterioles, not related to the capillary lesions; × 87.5.

FIG. 3.—Diabetes: arteriole, *A*, and venule, *V*, showing thickening, reduplication and disruption of the basement membrane of the venule in diabetes; × 87.5.

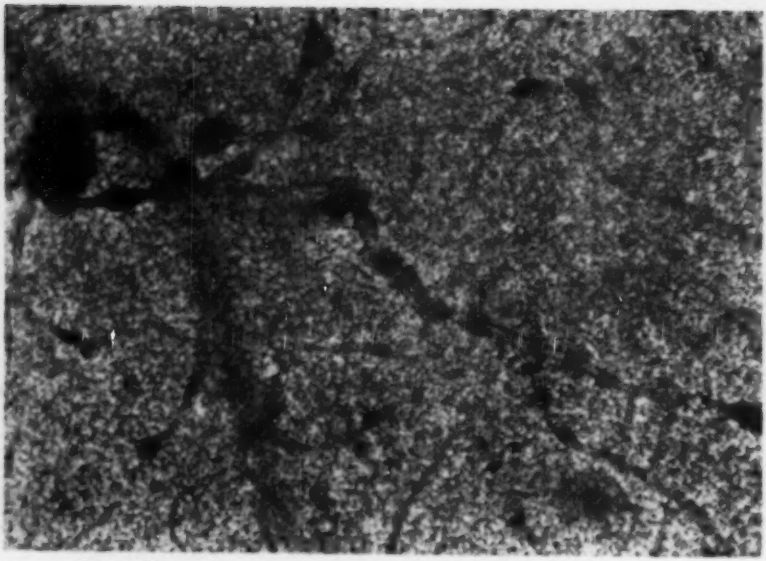

FIG. 4.—Dilatation and sacculation of an arteriolar capillary in malignant hypertensive vascular disease; × 30.

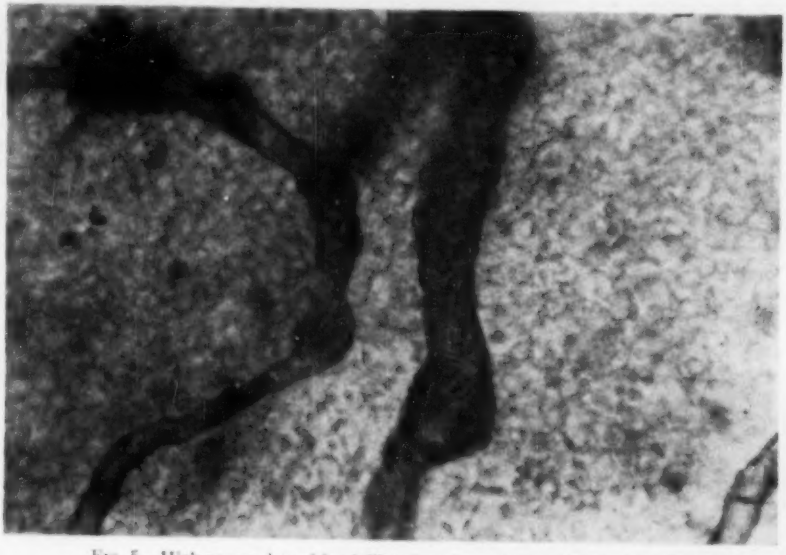

FIG. 5.—High power view of focal dilatation of arteriolar capillaries in malignant hypertensive vascular disease; × 300.

FIG. 6.—Reduplication and thickening of the basement membrane about a dilated arteriolar capillary in malignant hypertensive vascular disease; × 300.

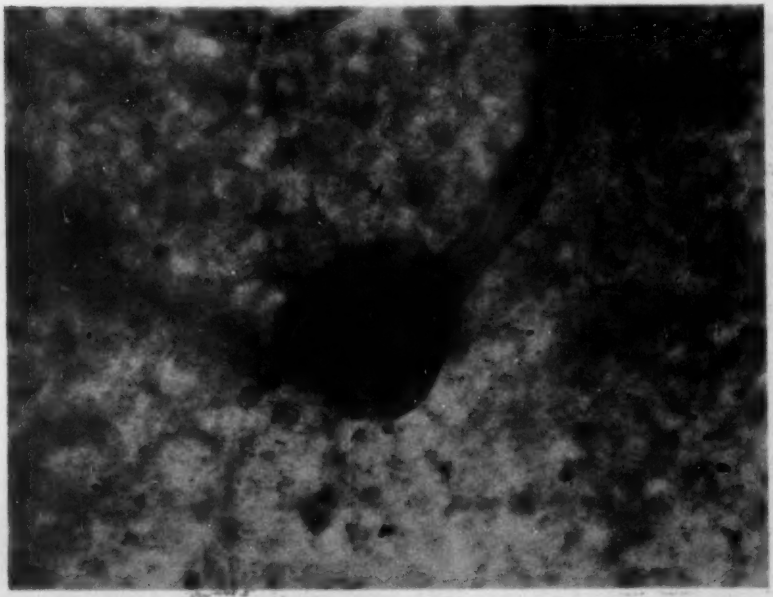

FIG. 7.—Cuff surrounding dilated arteriolar capillary cuff in malignant hypertensive vascular disease; × 300.

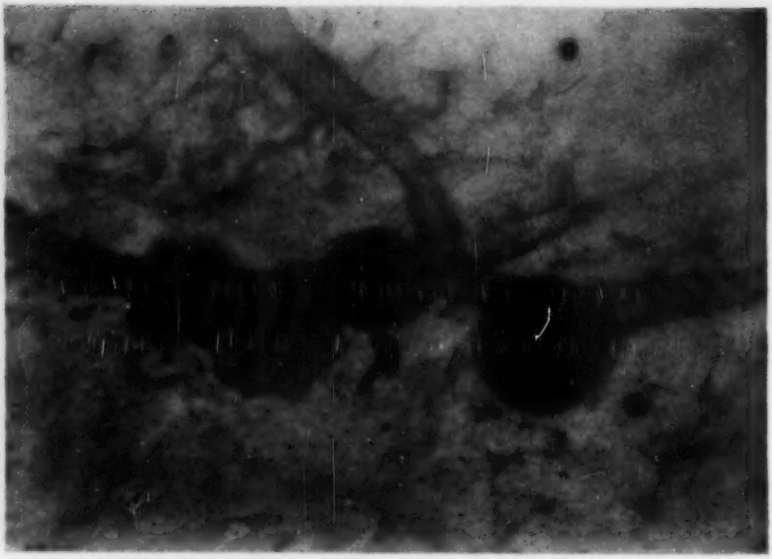

FIG. 8.—Stages in development of an arteriolar capillary cuff in malignant hypertensive vascular disease; × 300.

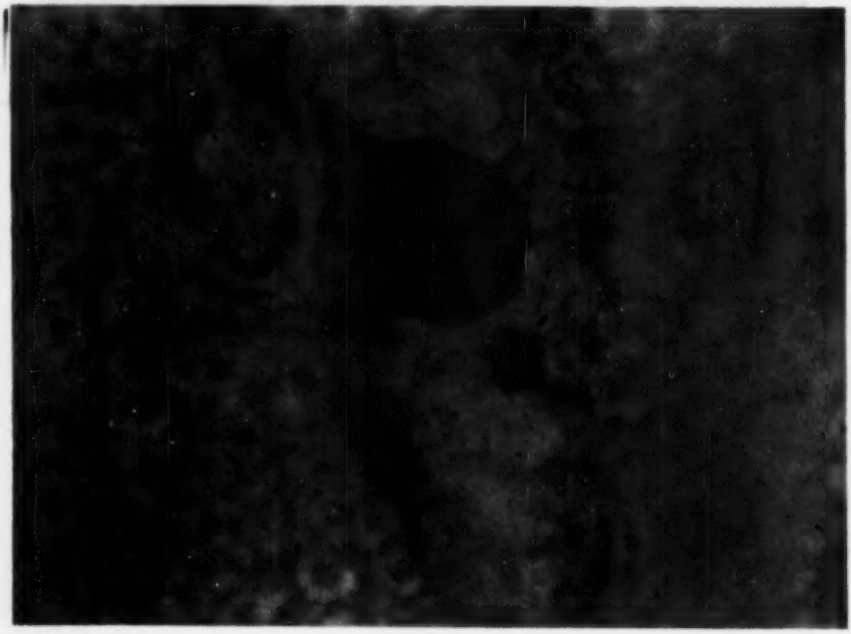

FIG. 9.—Early appearance of a microaneurysm in a capillary with thickened basement membrane and cuff in malignant hypertensive vascular disease; × 300.

Friedenwald. Eyes embedded in pyroxylin were found to be discolored after years of preservation and could not be used in this study. Of the group satisfactory for examination, 13 were eyes of diabetic patients and 40 were of patients who had succumbed to hypertensive vascular disease. On each patient a full autopsy, including the kidneys, had been performed. Of the group with hypertensive vascular disease, 11 had died in the malignant phase of the disease, and in each case malignant nephrosclerosis was found. Twenty-nine patients had the nonmalignant type, and in this group were included four with glomerulonephritis, two with periarteritis nodosa, two with lupus erythematosus and several with hydronephrosis and pyelonephritis.

It is our purpose to review briefly the capillary lesions in diabetes. We wish, however, to emphasize the lesions in hypertensive vascular

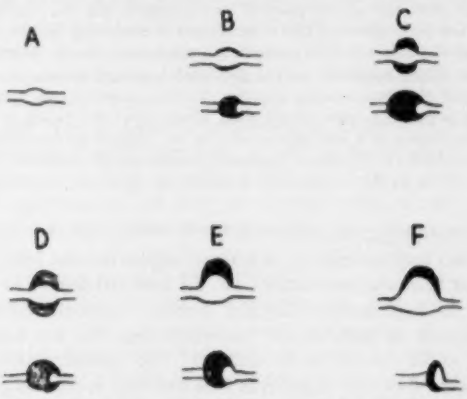

FIG. 10.—Schematic representation of development of arteriolar capillary lesions in malignant hypertensive vascular disease.

disease, especially since previous reports have been concerned particularly with the capillary lesions in diabetic retinopathy. In our group, numerous capillary lesions occurred in every case of proved malignant nephrosclerosis. In only one of 29 cases of nonmalignant hypertensive vascular disease were significant capillary lesions seen, and this was not a case of glomerulonephritis. We believe there are differences in the nature and distribution of the lesions as compared with those seen in diabetes. While the lesions are not as numerous as in diabetes, they are not confined to the area of the macula in the region of the disk, as in diabetes, but occur frequently throughout the retina and occasionally in the periphery. Finally, also, it would appear there are differences between the microaneurysms found in diabetes and similar lesions seen in hypertension, both in their structure and in the mechanism of their formation.

MICROSCOPIC STRUCTURE

Retinas of diabetic patients in each instance revealed capillary microaneurysms and sacculations of the capillary walls, similar to those described by Ballantyne, Friedenwald and Ashton. These lesions were seen predominantly in capillaries closely connected with small venules (fig. 1). Dilatation of venous capillaries was a prominent feature in all cases. In some areas, as in figure 2, near the disk, various stages of the disease process could be seen in a single tributary of a diseased venous capillary: dilatation, sacculation and microaneurysm formation. A striking feature of veins in diabetes of long standing was disruption of the continuity of the basement membrane (fig. 3). Venous capillaries in the area of such a diseased vein were frequently the sites of the most advanced capillary disease.

The retinas of all eyes in cases of the malignant phase of hypertensive vascular disease and pathologically proved malignant nephrosclerosis showed (1) dilatation and sacculation of some of the arterial capillaries (figs. 4 and 5), the dilatation resembling that seen in the capillaries in diabetes, and (2) a focal reduplication of the basement membrane at the point of its sacculation (fig. 6). Various stages in the growth and development of this reduplication or thickening lead to the formation of a lesion in the capillary wall resembling a microaneurysm in diabetes. Figure 7 represents a dilated capillary with a thickened basement membrane, surrounding which is a cuff of lighter-staining material. Various stages of this "cuff formation" can be seen in figure 8, with further focal dilatation of the capillary. This lesion gives the appearance of a microaneurysm (fig. 9). Figure 10 represents a concept of the development of the lesions appearing in the retinal capillaries in malignant nephrosclerosis, from the formation of a saccule, in *A*, to the final stage, in *F*.

COMMENT

Dilatation and sacculation of arterial capillaries and focal reduplication of their basement membranes are the essential lesions in the retinal capillaries in hypertensive vascular disease. Lesions resembling the microaneurysms in diabetes are frequently seen, but are not nearly as numerous as in the retina in diabetes. The retinal capillary lesions described were seen only in patients who had died in the malignant phase of hypertensive vascular disease and were absent in cases of benign hypertensive vascular disease and in hypertension associated with other diseases. They would seem to represent a specific disturbance in the retinal capillary circulation. The lesions are limited to the arterial capillary circulation, in contradistinction to the picture in diabetes, in which the lesions are predominantly in the venous capillary system. While these lesions probably result in capillary stasis, no evidence was found to indicate that they are responsible for the papilledema, hemorrhages or exudates seen in malignant hypertensive vascular disease. Assuming that the microaneurysm in diabetes and in hypertensive vascular disease may rupture, it is likely that the venous lesion of diabetes would result in more hemorrhage than the rupture of an arteriolar lesion of hypertensive vascular disease because of the active vasoconstrictor role of the arteriolar bed. Clinically, this is suggested by the slighter tendency to massive hemorrhage in the fundus of hypertensive vascular disease.

NYSTAGMUS

Its Diagnostic Significance

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THE TITLE is somewhat ambiguous; for this discussion to be as complete as is practical would have to include all forms of nystagmus.

From the standpoint of etiology three types of nystagmus are to be considered: an ocular, a central, or nonlabyrinthine, and a peripheral, or labyrinthine. Each is a separate entity, indicative of circumstances quite different one from the others, but all, in the final analysis, remarkably interdependent.

The ocular type is either spontaneous or induced. Central, nonlabyrinthine nystagmus is diagnostic, as well as symptomatic. The last of these three types, the peripheral, or labyrinthine, also is either induced or spontaneous, and these two forms, while related, have dissimilar diagnostic significance.

OCULAR NYSTAGMUS

Ocular nystagmus, in certain circumstances, has some localizing value. This is especially so in that ocular nystagmus has little, if any, relation to the vestibular nerves or nuclei or to any portion of the cortex. The localizing value of vertical nystagmus, on the other hand, is outstanding. This form of nystagmus can never be of peripheral, labyrinthine origin. It must be infratentorial, caused by lesions of certain structures, and is to be regarded as a symptom of release of the vestibular nuclei from cerebellar inhibition. Very rarely congenital ocular nystagmus of the pendular type will show a vertical component.

Ocular nystagmus, either pendular or jerky, is of dominant or sex-linked character, and should be considered a form of heredofamilial disease. The jerky form influences both optokinetic and induced vestibular nystagmus, while the pendular form has no relation to either the vestibular nuclei or the oculomotor nerves. This form of nystagmus, and its cortical and subcortical relations, will be discussed later.

Optokinetic nystagmus (induced ocular nystagmus), in its causation and in its physiologic and diagnostic relations, is largely connected with

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the cerebrum, rather than with the cerebellum. This is quite the opposite of other forms of nystagmus, exclusive of spontaneous ocular nystagmus.

In speaking of ocular nystagmus, one must consider undulatory as well as jerky nystagmus. Either one or the other may be present and still be ocular in nature. Undulatory (often described as pendular) nystagmus has to and fro oscillations which are practically equal in the two directions, both as to speed and as to amplitude of movement. Variations of all degrees are seen, and in certain circumstances the movements will increase or decrease both in rapidity and in amplitude. The patient will frequently discover the position of least movement and will hold his head and eyes in that position. He does this to improve his visual acuity, i. e., to minimize the extent of his disability. Many such patients obtain visual comfort by the wearing of prisms in each of their correcting lenses, the apex of the correcting prism being placed toward the deviation, or opposite the direction to which the head is turned. This permits the patient the same comfortable lateral position of the eyes, in a position of minimal nystagmus, and at the same time corrects the conspicuous head turning.

This deviation is such a common finding that it seems to refute a statement which appears frequently as to the cause of undulatory ocular nystagmus. It is commonly stated that ocular nystagmus is compensatory to, or arises from, central retinal scotomas. There is a relation between the two conditions, i. e., nystagmus and impaired vision, but it is hardly as simple as that.

Nystagmus will not appear unless central vision is lost in early infancy, before the fixation reflexes are developed. Apparently, some nystagmus will always appear if central vision is lost before 2 years of age. Nystagmoid movements, irregular and asymmetric in type, may develop when the vision is lost after this age, and before the age of 6, but this condition is not a true ocular nystagmus. Visual acuity must be bilaterally impaired. Unilateral central scotomas of early life, even congenital, are not uncommonly seen, and they show no nystagmus whatsoever. Visual acuity which is lost after the sixth year of life does not cause nystagmus.

There are other findings which further indicate that a central scotoma is not the cause *per se* of so-called congenital nystagmus. The undulatory movements of the eye, however, resulting from this type of nystagmus may not appear until weeks after birth.

Occasionally children with an ocular nystagmus will also show lateral or vertical movements of the head. These are compensatory, because they occur contrariwise to the ocular movements. Slow motion moving pictures have demonstrated that. If the head is held so that it cannot be moved, the nystagmus will reappear or become aggravated. Older children and adult patients will demonstrate a similar correlation.

If one can move a card to and fro in front of the eyes until it matches the speed and amplitude of the movements of the eyes, then the visual acuity will be appreciably improved, confirming the presumption that the head movements also appear unconsciously for the improvement of vision by such a compensation or stabilization. This seems to indicate that the nystagmus not only does not compensate for the loss of vision, but actually makes the visual acuity worse.

This is a rather important problem. Spiegel and Sommers [1] stated: "Since a sharp image in the fovea is not possible, the mechanism is defective, with a nystagmus as a consequence." There is no doubt that the greatest degree of nystagmus appears in eyes which have the greatest amount of visual loss. The gross, searching nystagmus of the blind and the practically blind is common knowledge. Complete color blindness, albinism, bilateral congenital cataract—these, and many other conditions, some inflammatory in nature, are seen as the apparent cause of the nystagmus. Idiocy and imbecility are also to be included as etiologic factors. Certainly there is much evidence to show that ocular nystagmus is accompanied with defects in central vision, but that it is not directly caused by the loss of visual acuity. Actually, the nystagmus exaggerates the impairment of visual acuity. The interpretation first suggested by Cogan [2] is the only logical one for these forms of nystagmus. That interpretation will apply in cases of hereditary nystagmus, latent nystagmus and the nystagmus of so-called spasmus nutans. He spoke of these forms as "an ataxia of the eye muscles" and stated that it results from "the failure of the normal, tonic innervation from the macula." The extraocular muscles have no propioceptive end organs. The retina furnishes, in place of this lack of sensitivity, positional information as to the eyes. Because of the central impaired vision, this information is wanting—hence a failure in restraining the various cerebral and cerebellar impulses that act on the ocular muscles in conjugate movements. Almost every person with ocular nystagmus will exhibit in various positions vertical, horizontal, oblique and rotatory forms, suggesting this absence of control. Ordinary pendular nystagmus in the midline with fixation may change to a jerky nystagmus of all possible degrees when the patient is looking to the right or to the left. These variations, in the extremes of the concomitant movements, are rather analogous to the nystagmus which one sees with eccentric fixation in the normal subject. This physiologic nystagmus of gaze, or end position nystagmus, is the normal analog of that which has just been described.

1. Spiegel, E. A. and Sommer, I.: Neurology of the Eye, Ear, Nose and Throat, New York, Grune & Stratton, Inc., 1944.

2. Cogan, D. G.: Neurology of the Ocular Muscles, Springfield, Ill., Charles C Thomas, Publisher, 1948.

Exaggerated end point nystagmus has an interesting significance in two conditions—first, as the sign of minimal paralysis of an extraocular muscle, or of partial or incomplete recovery from a paralysis; and, second, as a common accompaniment of a state of acute weakness, such as is seen in the Guillain-Barré syndrome. A certain moderate degree of this nystagmus is to be considered normal.

Induced ocular nystagmus, so-called optokinetic nystagmus, is an ocular reflex response depending on several different situations. Experimental work indicates that there is probably a centripetal pathway to the occipital lobe. Because the optokinetic nystagmus is a manifestation of the following reflex, or reaction, a fixation reflex is necessary. That demands the presence of a certain degree of function of the visual pathways, i. e., a certain amount of anatomic integrity of the visual tracts. The following reflex accounts for the slow phase of the nystagmus and occurs through the centripetal optomotor pathways to the occipital lobe. The quick phase of the nystagmus is the return to normal fixation. The slow phase is more or less involuntary, whereas the quick phase is voluntary and is to be identified with volitional gaze. The frontal lobe and the intercortical connections between the centripetal and the centrifugal pathways probably have to do with the quick component. Decerebration in animals does not prevent optokinetic nystagmus. This, with other findings, suggests the probability that some other region, perhaps the superior colliculus, functions as a visual center in animals. In man, however, an intact area striata of the occipital cortex is necessary because the slow phase of optokinetic nystagmus is impossible without a certain amount of visual acuity. The degree of visual acuity necessary for the development of the nystagmus is proportionate, in terms of visual angle, to the stimulus used for its development and to the intensity of illumination present during the testing.

The interpretations of induced ocular nystagmus are also modified or related by the absence or presence of cogwheel movements, or *mouvements saccadés*. This relation to cogwheel movement is natural in that this pathologic movement is of itself a disturbance of the following reflex. In cases of unilateral cogwheel movement with homonymous hemianopsia the cogwheel movement is opposite the hemianopsia. Right hemianopsia indicates, of course, a lesion on the left side. Absence of optokinetic nystagmus in the presence of cogwheel movement suggests (*a*) when bilateral, an encephalitis; (*b*) when unilateral, and with the presence of hemianopsia, a lesion of the middle or posterior part of the optic radiation, in the direction of the abnormal movement contrary to the position of the hemianopsia, i. e., homolateral with the cerebral lesions, and (*c*) without hemianopsia, a lesion in the region of the angular gyrus, again homolateral and toward the side of the lesion.

The slow or the quick phase, one or the other, may be absent. Occasionally one finds absence of the quick phase of both optokinetic nystagmus and induced vestibular nystagmus, the two defects occurring simultaneously as tested. This suggests that certain centers in the brain stem are common to both vestibular and optokinetic nystagmus and also are identical with, or connected with, the pontile centers for conjugate lateral eye movements. It is rather certain, also, that the cortical pathways and/or centers for the slow phase of induced ocular nystagmus are the same as those for conjugate lateral and up and down movements.

In the consideration of optokinetic nystagmus as to both development and significance, one must remember that the presence or absence of hemianopsia is not the significant primary factor. Disturbances in the optic pathways and the effect of these on the following reflex are the basic faults. The following movement can be intact, even with an actual central scotoma, and certainly so with a questionable central scotoma. Optokinetic nystagmus can be developed if part of the macula still functions. Conversely, the absence of the following movements does not prove the absence of a functioning macula, since other factors may be responsible. The following movement is absent in gaze paralysis, is absent in oculomotor palsy of peripheral type, is frequently absent with spontaneous ocular nystagmus of hereditary nature, i. e., fixation nystagmus, and is said to be frequently absent in functional blindness, such as one sees with the amblyopia of squint.

Optokinetic nystagmus may halt or reverse the direction of spontaneous central, nonlabyrinthine nystagmus or of induced labyrinthine nystagmus. When one recalls that the three important factors in these forms of nystagmus are a fixation reflex, a following reflex and a correcting reflex, this finding is logical. The fixation reflex is the slow phase; the corrective reflex is the rapid component. The following reflex is also a part of the slow phase. There is some inconsistency here in that the role of the cerebellum in induced ocular nystagmus is controversial; in fact, the cerebellum may be wholly unrelated, and some of the other types of nystagmus mentioned can be modified by optokinetic nystagmus. The significance of induced ocular nystagmus, of course, is connected with the rotation of the drum toward the side of the lesion.

The figure shows a slide [3] designed for the development of induced ocular nystagmus. The carrier is of such a size that it will fit into the frame of a standard phoroptometer. Firm support of this carrier is necessary so that the patient can be carefully observed as the slide is moved from side to side or up and down. The moving portion of the slide is 22 to 24 inches (55.9 to 60.9 cm.) long. The black vertical lines are ¼ inch (0.64 cm.) wide and have 3½ inches (8.89 cm.) clearance between

3. The slide was designed by Dr. Oscar V. Batson, Professor of Anatomy, University of Pennsylvania Graduate School of Medicine.

them. These distances and sizes were developed through trial and error methods until a slide was designed which induced the greatest amount of nystagmus in the shortest time, even when visual acuity was appreciably impaired.

In general, an optokinetic response is normal when a lesion under question, accompanied with hemianopsia, is in the optic tract; in fact, normal induced ocular nystagmus with hemianopsia has no localizing significance. Hemianopsia accompanied with abnormalities in induced ocular nystagmus indicates a cerebral lesion, and, rather likely, one anteriorly placed.[4] Lesions with motor aphasia have been reported with pathologically induced ocular nystagmus. A comparison of the effect of lesions of the frontal lobe and those of the occipital lobe on induced ocular nystagmus reveals the presence of a "lasting" effect of lesions of the occipital lobe. In lesions of the frontal lobe the pathologic situations seem to be compensated for rather early. Lesions in the posterior half of the cerebrum, whether or not accompanied with hemianopsia, and especially when related to the angular gyrus, are very likely to cause defects in induced ocular nystagmus. Alexia, aphasia,

Batson's slide for induction of ocular nystagmus.

agraphia, finger agnosia, inability to read and inability to perform even simple calculations have been reported with this type of nystagmus, and with such lesions. One must remember that alexia is the result of a left-sided lesion in a right-handed person.

CENTRAL, NONLABYRINTHINE NYSTAGMUS

Central, nonlabyrinthine nystagmus is next of importance. The relation which exists between this and vestibular nystagmus, spontaneous or induced, is not too clearcut, except that such a relation is present and, furthermore, is dominant.

Some authors speak of this nystagmus from disease of the central nervous system as a vestibular form. This designation is not quite proper. One or two common findings seem to support such a difference of opinion. Vertical nystagmus was mentioned earlier. This form of nystagmus can never be the result of spontaneous or induced stimulation of the labyrinth. Instead, it is due probably to disturbances of the vestibular nuclei. It means almost certainly a pathologic change in the

4. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1946.

brain stem, infratentorial always; and the pathologic process, furthermore, should be of a destructive nature, such as would be seen with an expanding midline cerebellar tumor. It is rather interesting that Parinaud's syndrome of paralysis of upward gaze has a significant etiologic, anatomic and physiologic relation to vertical nystagmus. This is similar to disturbances in the centers for conjugate movements observed in analyzing horizontal nystagmus and in considering the pontile center or locus for lateral conjugate gaze.

A second reason for questioning the statement is the frequency with which one finds nystagmus with certain vascular lesions of the brain stem. While the effect of these lesions is quite possibly on the vestibular nuclei as these are distributed in the cerebellum and in the brain stem, or on the internuclear pathways, as just mentioned with the medial longitudinal bundle, autopsies do not confirm that assumption consistently. Nystagmus has been seen with aneurysm of one or both carotid arteries, and it has been reported with an aneurysm of the posterior inferior cerebellar artery. The horizontal nystagmus, spontaneous and of the jerky type, which one sees early in a case of extradural temporosphenoidal abscess without accompanying lesion in the labyrinth is certainly not labyrinthine in type.

Central, nonlabyrinthine nystagmus will be seen, at times, obeying all the laws associated with the supratentorial forms of conjugate deviation. Since the slow phase of a jerky nystagmus is the pathologic one, and the quick phase is an attempt to return the eyes to normal frontal fixation, one must also consider the slow phase of that form of nystagmus just mentioned, as one would consider the direction of the deviation in cases of conjugate deviation, to the right or to the left. When this slow phase is caused by a supratentorial lesion, it must be irritative in origin; when it develops from an infratentorial lesion, it must be destructive in origin.

Central, nonlabyrinthine nystagmus of diffuse pathologic origin may be of horizontal, vertical, rotatory or mixed type. Its quick component is most frequently toward the diseased side. The regions responsible are the medulla, the pons and the midbrain.

Vertical nystagmus, central, and hence nonlabyrinthine, with the quick component upward, and augmented by upward gaze, is frequently an early manifestation of pressure on the lamina quadrigemina, such as might be caused by a tumor of the anterior portion of the cerebellum or by a tumor of the most posterior portion of the third ventricle. Pressure on the lamina quadrigemina, for a time, will cause a paralysis of vertical ocular movements, the so-called Parinaud syndrome. Such a lesion may occasionally give rise to nystagmus retractorius as well. Vertical nystagmus may also appear, with or without other symptoms, with a tumor of the pineal body.

Vertical nystagmus also has an interesting relation to the frontal lobe. Spiegel and Sommer showed that the cortical innervation of vertical eye movements is possible without the mediation of the vestibular nuclei or of the posterior longitudinal bundle. In their experiments, these observers found that stimulation of the frontal lobe, after section of the posterior longitudinal bundle—in fact, after total transsection of the brain stem behind the midbrain—still produced vertical eye movements. The rhombencephalon is therefore not necessary for the production of cortically induced vertical movements. Spiegel and Sommer stated further:

> Destruction of the central gray matter in the cranial part of the mesencephalon and the pretectal region induces loss of upward and downward movements on cortical stimulation. Small lesions of this region may be followed by various partial disturbances of the vertical ocular movements—e. g., loss of conjugate movements in one direction only, appearance of skew deviation on cortical stimulation, loss of vertical movements on stimulation of certain cortical areas (e. g., occipital lobes) only.

While Godlowski assumed that the direct connection between the reticulate substance of the tegmentum and the nuclei of the ocular muscles is sufficient for the cortical innervation of conjugate upward movements, the experiments of Spiegel and Sommer indicate that the impulses for upward, as well as for downward, movements make their way over systems within, or closely adjacent to, the central gray matter before reaching the nuclei for the ocular muscles.

Extirpation of the roof of the midbrain (tectum) shows that this is not an indispensable part of the system that transmits impulses for vertical ocular movements from the frontal oculogyric centers. Paralysis of vertical conjugate movements in diseases of the dorsal part of the mesencephalon, with nuclei for the ocular muscles intact, should therefore be regarded as a symptom of a lesion in the region about the aqueduct, or of closely adjoining regions, including involvement of the nuclei in the region of the posterior commissure.

Cogan's reported types of internuclear ophthalmoplegia included the syndrome of weakness of conjugate movements accompanied with nystagmus. This form of internuclear ophthalmoplegia is seen occasionally with vascular lesions, as well as with those two common causes of lesions in the medial longitudinal bundle, i. e., multiple sclerosis and encephalitis.

Lesions of the central nervous system which frequently produce horizontal and horizontal-rotatory nystagmus are multiple sclerosis, by involvement of the vestibular nuclei and pathways in this disease; syringobulbia, which affects the floor of the fourth ventricle; encephalitis and degenerations; tumors and abscesses, and the vascular anomalies in the cerebellopontile angle. Abscesses (otologists state) are prone to

produce a postural nystagmus, i. e., one that varies with different positions of the head. It is quite probable that this is due to postural labyrinthine stimulation and the effect of this on the nystagmus of a cerebellar abscess. A similar relation has been seen in cases of severe cranial trauma when the degree of nystagmus is dissimilar one side from the other. This furnishes a rough approximation to lateralization; for the side is indicated by the direction of the quick component of the nystagmus. Frequently, however, as the quick component is commonly in the direction of gaze, this direction has no lateralizing value.

The relation of the cerebellum to nystagmus is interesting. Cerebellar lesions have, frequently, relatively little influence on caloric induced nystagmus (Bárány test). On the other hand, nystagmus is a common symptom of cerebellar disease. Experimental removal of the cerebellum does not produce spontaneous nystagmus, nor does this prevent the formation of nystagmus. (These factors, as just stated, suggest that other structures in close proximity to the cerebellum, or in contiguity with it, are more significant than the cerebellum itself.)

LABYRINTHINE NYSTAGMUS

The differentiation of central nystagmus from labyrinthine nystagmus is interesting, and at times important. Labyrinthine nystagmus tends to decrease and to disappear as peripheral, middle or inner ear suppuration continues, while with cerebellar abscess it progresses, though with this condition nystagmus may also occur early and disappear early. The cerebellum is probably involved on the homolateral side when there is complete lack of outward and inward pointing on turning and douching. Spontaneous nystagmus lasting for days with general symptoms, such as vertigo, staggering gait and asynergia, is more than suggestive of cerebellar involvement. In this cerebellar control of nystagmus each side of the cerebellum is to a certain extent concerned with all positions of the eye, but this control is greater in the direction of the same side and less to the opposite side.

With respect to this, Bing[5] in speaking of cerebellar control of oculomotor responses, stated ". . . in early stages of cerebellar tumors and hemorrhages, etc., there may, on the contrary, occasionally be observed a conjugate deviation to the diseased side. In such instances we are dealing with an irritative symptom." This may be produced experimentally; i. e., Bárány's test applied to a lightly anesthetized patient produces a conjugate deviation to the irritated side, instead of nystagmus. The abolition of consciousness seems to inhibit the quick

5. Bing, R.: Compendium of Regional Diagnosis in Affections of the Brain and Spinal Cord, ed. 3, St. Louis, C. V. Mosby Company, 1927, p. 147; Textbook of Nervous Diseases, translated and enlarged by Webb Haymaker, St. Louis, C. V. Mosby Company, 1939.

component, or automatic return of the eyeball toward its normal position—a movement which is essentially a part of the nystagmus cycle.

It is generally possible to distinguish cerebellar nystagmus from the labyrinthine type. There are three possible criteria: 1. If the nystagmus is toward the diseased side, it may be due to circumscribed labyrinthitis or to cerebellar abscess; but if after operation on the labyrinth the nystagmus persists toward the diseased side, the cause should be sought in a cerebellar lesion. 2. If a rotary nystagmus is directed toward the well side and the labyrinth is without a reaction, the nystagmus may be due to either the labyrinth or the cerebellum. In this case, diagnosis is impossible before operation on the labyrinth. 3. If the nystagmus is due to disease of the labyrinth, it should disappear after two or three days; but if due to cerebellar disease it will remain unchanged, or it may change to the opposite, or diseased, side, in which case its cerebellar character may be diagnosed with certainty.

Smith,[6] in discussing the same problem, claimed an even greater diagnostic value for nystagmus, in that it would assist in differentiating labyrinthine from cerebellar stimulation and these, in turn, from nystagmus due to cerebral or temporosphenoidal abscess.

> When the clinical picture and laboratory tests exclude everything except brain abscess, the vestibular examination might indicate whether such an abscess is in the cerebellum or in the temporal lobe. The ability to elicit vertigo and past-pointing after stimulation will eliminate the cerebellum and suggest the temporosphenoidal lobe as the possible site of trouble.

In general, this form of central, nonlabyrinthine nystagmus is a symptom closely allied to infratentorial lesions and resembles peripheral, labyrinthine nystagmus in that anatomic structures common to, or necessary for, one type are necessary for the other. These include centrifugal tracts from the frontal lobe to the internal capsule; corticofugal tracts from the occipital lobe; the cortical and subcortical origins of these fibers, the vestibular nuclei and the other nuclei of equilibrium and vertigo; the cerebellum (remembering, however, that at all times this is a reflex organ, and it makes little difference whether the central, the centrifugal or the centripetal part of the reflex arc is broken); the nuclei of the ocular muscles; the anterior horn cells of the spinal cord; the pontile and cortical centers for conjugate lateral ocular movements; the medial longitudinal bundle; the vestibulocerebellar tract, and the vestibulospinal tract.

The centers and the pathways for the two phases of nystagmus, the fast and the slow, also differ one from the other. The fast phase is

6. Smith, M.: Laryngoscope **34**:534 (July) 1924.

the more primitive of the two and is probably not dependent on centers higher than the vestibular nuclei. The slow phase is the pathologic one throughout and is dependent on many and varied factors.

The localization of vestibular nystagmus is as follows: The rhythm of nystagmus is of central origin. The cortical area responsible for it is to be sought in the rhombencephalon. The related regions are the cerebrum, the diencephalon and the substantia reticularis rhombencephali; even the nuclei of the ocular muscles may be the site of origin not only of the mechanisms that innervate the slow component, but also of those that actuate the quick component, of the nystagmus. Therefore, for the genesis of both phases of vestibular nystagmus, the afferent fibers from the labyrinth, the efferent nerves to the ocular muscles and the part of the central nervous system lying between the afferent and the efferent paths are sufficient. This explanation oversimplifies vestibular nystagmus to a rather absurd degree, but for the purposes of this paper it is correct. One other point is relevant here. Factors present in the peripheral end organ play, at the most, only a minor supporting role in the origin of the quick component. That is to be looked for chiefly in the central nervous system.

Induced labyrinthine nystagmus, caused by douching with hot or cold water or by turning, has a very definite relation to ocular symptoms. The three semicircular canals of the labyrinth can be activated separately and independently. The technic and interpretation of the findings are essentially neuro-otologic.

The clinical tests result in many and varied responses. The importance of these tests in cases of supratentorial lesions is frequently controversial. Perhaps the greatest value in differentiating supratentorial from intratentorial lesions lies not so much in the certain diagnosis of a supratentorial pathologic process as the elimination, by this test, of an infratentorial lesion in any case under consideration. The tests as carried out consider the development or absence of nystagmus, inversion of the nystagmus, appearance of conjugate deviation rather than nystagmus and the observation of defects in past pointing. Vertigo, in its type and degree, can be quite significant in the analysis.

Destructive lesions of the labyrinth prevent the development of the various types of induced nystagmus. Lesions of the vestibular nerve or nuclei show a characteristic decrease, or even absence, of vestibular nystagmus. This is shown beautifully in tumors of the cerebellopontile angle. The normal vestibular responses may be absent in cerebellar disease, or the normal responses may be altered by pressure on the brain stem. Changes in posture are especially important here. Cogan stated that postural nystagmus is present with 80 per cent of tumors in the posterior fossa but is never found with tumors in the middle or anterior fossa.

The various reports of changes in the vestibular reactions from cerebral lesions have been questioned, as stated. Abscence of the quick phase of induced vestibular nystagmus has been reported with lesions of the temporal lobe. It is interesting that in such situations the fast phase of optokinetic nystagmus is also likely to be absent. Another cerebral sign is the so-called doll's head movement. In these movements voluntary ocular gaze is lost, but a full deviation of the eyes occurs with vestibular stimulation, in spite of this pseudo-ophthalmoplegia. This response is supposed to be diagnostic of pathologic changes in the basal ganglions of the cerebral hemisphere. It has significant lateralizing value when present.

CONCLUSIONS

In general, nystagmus is an ocular sign common to many conditions. Some forms of nystagmus are purely ocular, while others are as definitely the result of pathologic conditions of the central nervous system or are related to such lesions through their peripheral labyrinthine connections. As Walsh[7] said, "the literature is voluminous and frequently so replete with hypotheses as to be completely beyond comprehension." That which has just been detailed has, it is hoped, real clinical significance; for too frequently the diagnosis of an intracranial lesion is an ophthalmologic problem.

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7. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947.

PREPARATION OF OPHTHALMIC SOLUTIONS WITH SPECIAL REFERENCE TO HYDROGEN ION CONCENTRATION AND TONICITY

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NEW ORLEANS

A GREAT deal has been written in the ophthalmologic literature about the importance of the hydrogen ion concentration and the tonicity of ophthalmic therapeutic solutions. Much of the published material is not in a form that is readily usable by the practicing ophthalmologist. We decided to investigate the practical limits of variability of these two factors and to evaluate their importance. Our aim is to present here what we believe to be the best solutions, based on present knowledge, for practical prescribing and feasible compounding of solutions containing most of the frequently used ophthalmic drugs.

Recently, Swan [1] summarized the factors known at present which influence the permeability of the cornea by therapeutic agents. He pointed out that the tonicity of the tears, as reported by various workers in terms of the sodium chloride equivalent, varies from 0.9 to 1.4 per cent. He stated elsewhere [2] that solutions with tonicity below that of a 0.5 per cent or above that of a 2 per cent sodium chloride solution produce damage to the corneal epithelium. From simple observation of solutions commonly used in the eyes of patients, it would seem that the range of variation in tonicity which is safe for clinical use in the conjunctival sac of the living subject may be much greater than this. Certainly, it can be definitely stated that the most desirable range of tonicity for therapeutic solutions would be the range which has been found for the tears themselves, as the tonicity of the solution has no effect on the rate of permeation of the cornea unless the solution is so hypertonic or

1. Swan, K. C.: Pharmacology and Toxicology of the Cornea, Arch. Ophth. **41**:253-275 (March) 1949.

2. Swan, K. C., and White, N. G.: Permeability: I. Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043-1058 (Sept.) 1942.

hypotonic that it will damage the corneal epithelium. For these reasons, we believe that an ophthalmic therapeutic solution is perfectly acceptable if it has a tonicity equivalent to sodium chloride solutions of between 0.9 and 1.4 per cent (freezing point depression, — 0.56 to — 0.80 C).

The general opinion can be found in the literature that the hydrogen ion concentration of a solution is one of the most important factors in determining the sensation the solution will produce when instilled into the conjunctival sac. The only one who has recorded a systematic investigation of this factor is Lipschütz.[3] He used phosphate buffers and evidently tested only his own eyes, since he gives no figures on the number of persons tested. He stated that solutions with a p_H of 6.6 to 8 would be nonirritating. Anything above or below this range he considered irritating. Arrigoni, Fischer and Tozer[4] considered solutions within the range of p_H 6.5 to 7.8 nonirritating.

TABLE 1.—*Sensibility of the Conjunctival Sac and Cornea to Variations in the Hydrogen Ion Concentration of Isotonic Phosphate Buffers*

p_H	Number Tested	Mild, Transient Burning or Irritation	Transient, Definite Discomfort	No Discomfort	
				No.	%
5.4	18	4	9	5	27.8
5.6	27	13	3	11	40.7
6.0	18	4	7	7	38.8
6.6	26	3	0	23	88.5
7.08	27	0	0	27	100.00
8.7	26	3	0	23	88.5

Because it would be advisable for pharmaceutic reasons to use solutions much more acid than the lowest value Lipschütz and others have stated as compatible with comfort, we investigated this matter further. Using medical student volunteers and isotonic phosphate buffer solutions modified from those described by Sorensen,[5] we obtained results that are in approximate agreement with those given by Lipschütz (table 1). Gifford[6] at one time questioned the general applicability of these findings, and reflection on solutions in common use raises doubts as to the conclusion that this range of the p_H within which no discomfort is experienced applies to all solutions.

3. Lipschütz, H.: Ueber die Bedeutung der Wasserstoffionenkonzentration in Bindehautsack, Klin. Monatsbl. f. Augenh. **82**:763-769, 1929.

4. Arrigoni, L.; Fischer, L., and Tozer, G. A.: Ophthalmic Zinc Sulfate Solutions, Arch. Ophth. **26**:852-858 (Nov.) 1941.

5. Sorensen, cited by Phillips, M.; Clark, W. M., and Cohen, B.: The Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1928, p. 210.

6. Gifford, S. R.: A Hand-Book of Ocular Therapeutics, ed. 2, Philadelphia, Lea & Febiger, 1937.

We tested 12 volunteers (resident physicians) with a 2.2 per cent boric acid solution of p_H 5.1. The p_H was determined on the day of the tests. None of those tested experienced the slightest feeling other than a sensation of fluid being in the eye.

Arrigoni, Fischer and Tozer [4] proposed a boric acid–sodium acetate buffer solution for zinc sulfate which they stated is stable while having a p_H of 6.75. They gave an acid stock solution and an alkaline stock solution which may be mixed in proper proportions to yield the desired p_H. They did not state the proportions. By mixing these two stock solutions, we prepared two test solutions. One had a p_H of 5.65 and one a p_H of 6.75, and each was prepared so as to contain all the ions in each stock solution. This was done to minimize the influence of the individual ions on the results. Both test solutions contained 0.125 per cent zinc sulfate. Theoretically, the former solution was sufficiently acid

TABLE 2.—*Sensibility of the Cornea to Variations in p_H of Isotonic Solutions of Zinc Sulfate Prepared from Those Recommended by Arrigoni, Fischer and Tozer* [4] *

p_H	Mild, Transient Burning or Irritation	Transient but Definite Discomfort	No Sensation
5.65	8.4	12.5%	79.2%
6.75	20.9	12.5%	66.7%

* Twenty-four persons were tested.

that there should have been many more complaints on its being instilled. We put a different solution into each eye of the same volunteer. The purpose of the test was explained, but every effort was made to avoid any form of positive suggestion.

From the solution of p_H 5.65, 79.2 per cent experienced no sensation, 8.4 per cent complained of mild, transient discomfort and 12.5 per cent complained of definite but transient discomfort. From the solution of p_H 6.75, 66.7 per cent experienced no sensation, 20.9 per cent complained of mild but transient discomfort and 12.5 per cent complained of definite but transient discomfort (table 2). The results are statistically significant and amazingly similar. Certainly, there is nothing to indicate that the zinc sulfate solution with the higher p_H is more desirable.

When these results are all considered, it is apparent that Lipschütz was approximately correct in his conclusions regarding the importance of the hydrogen ion concentration of solutions of phosphate buffers in relation to the sensation they produce when instilled into the conjunctival sac. It is also apparent that conclusions reached with phosphate

buffers cannot be applied to solutions of other composition. The p_H values which will prove irritating or nonirritating must be determined separately for each substance and for each combination that may be used in an ophthalmic therapeutic solution. For some types of solutions (e. g., 2 per cent boric acid), it seems that the p_H actually is not of too much importance in relation to the sensibility of the cornea and conjunctiva, if the extremes of the p_H value beyond which epithelial damage occurs are not exceeded. With other combinations of substances (e. g., phosphate buffer solutions) in solutions, it seems that the p_H may make considerable difference in the sensation produced. It is thus obvious that the most important factor in determining the sensation which a solution produces is the chemical identity of the substances in the solution and the combination they are in. It does not appear possible to give a range of nonirritating p_H values which will apply to all ophthalmic solutions.

According to Friedenwald and associates,[7] the p_H of ophthalmic therapeutic solutions may be varied safely between 4.5 and 11.5. The most desirable p_H for any given solution will vary from solution to solution. For those intended as tear substitutes p_H 7.2 to 7.4 is the most desirable. The work of Fischer[8] would seem to indicate that most of the alkaloids should be buffered to p_H values indicating slightly greater alkalinity than p_H 7 in order that they will more readily penetrate the cornea.

The chemical stability of a drug in a solution which is to be dispensed to a patient or kept on hand for some time cannot, however, be overlooked. Hind and Goyan[9] have justifiably stressed this point. Although we ran no quantitative tests for stability, a few solutions which we prepared containing the acid salts of alkaloids and having a p_H higher than 7 were grossly unstable. Hind and Goyan[9] suggested a compromise between conflicting p_H values for maximum stability in solution and maximum physiologic effectiveness. Certain drugs can be dissolved only in solutions with a p_H of between 5 and 6 and be stable to a desirable degree. A 2.2 per cent boric acid solution is recommended for these drugs. Although this is not a buffer solution, it serves the purpose of a vehicle in which the drug is stable and which in itself is not irritating. For those substances which are stable enough at a p_H

7. Friedenwald, J. S.; Hughes, W. F., Jr., and Herrmann, H.: Acid-Base Tolerance of the Cornea, Arch. Ophth. **31**:279-283 (April) 1943.

8. Fischer, F. P.: Ueber die Durchlässigkeit der Hornhaut für Alkaloide, Arch. f. Augenh. **104**:121, 1931.

9. Hind, H. W., and Goyan, F. M.: New Concept of the Role of Hydrogen Ion Concentration and Buffer Systems in Preparation of Ophthalmic Solutions, J. Am. Pharm. A. (Scient. Ed.) **36**:33-41 (Feb.) 1947.

near, but slightly below, 7, they recommend a phosphate buffer solution. We found this solution to give satisfactory values of hydrogen ion concentration after therapeutic amounts of the salts of the various drugs tested had been added. The p_H of these solutions was taken with a Beckman glass electrode p_H meter about three hours after they were prepared and, again, twenty-seven days later. Solutions of all those drugs which we recommend to be placed in this phosphate buffer solution were clear and free of precipitate, mold growth or color after standing for the twenty-seven days (tables 3, 5 and 6, on phosphate buffers).

The situation is actually much simpler than it seems at first. With the exception of phenacaine, cocaine, physostigmine and zinc sulfate, nearly all the substances which the druggist is called on to compound into solutions in the ordinary pharmacy should be dispensed in a phos-

TABLE 3.—*p_H of Various Substances When Prepared as Recommended*

	p_H (6.72)
In Hind and Goyan phosphate buffer:	
Atropine sulfate 1%	6.72
Homatropine hydrobromide 4%	6.68
Scopolamine hydrobromide 0.5%	6.71
Eucatropine hydrochloride 8%	6.70
Ephedrine sulfate 2%	6.67
Pilocarpine nitrate 1%*	6.38
Pilocarpine hydrochloride 2%	6.2
In other solutions:	
Carbachol (carcholin) in 1:3,500 benzalkonium chloride	6.82
Zinc-glycerin-boric acid solution (0.1% $ZnSO_4$)	5.75
Cocaine hydrochloride 3%, sodium lactate 1%	5.30

* It is recommended that the hydrochloride be used instead of the nitrate because of the incompatibility of the latter with benzalkonium chloride.

phate buffer. The rest of the drugs which are commonly used are put out by the manufacturing pharmaceutical houses already in solution and are so dispensed. We tested the p_H of some of the more important ophthalmic solutions which the druggist receives already compounded and found that all of them were quite acceptable, except as noted in table 4. Calculations based on their published formulas also showed all of them to be of acceptable tonicity, except as noted in the same table.

Although careful consideration may be given to the tonicity and hydrogen ion concentration of a buffer solution which is to be used as a vehicle, the fact that the tonicity is often changed after the desired drug is added is often overlooked. Sprowls [10] has called attention to this and offers a solution of the problem in the form of a table. This

10. Sprowls, J. B.: Simple Fixation in the Use of Isotonic Diluting Solutions, J. Am. Pharm. A. **10**:348-351, 1949.

table shows the quantity of water required to dissolve that amount of the drug which will give a 1 per cent concentration in the final solution, when a stock buffer solution is added to make 1 ounce (30 cc.). This results in a preparation which has a desired, known tonicity. This is one way of solving the dilemma, but we believe that even this amount of care in calculation is not necessary, or even particularly desirable. If the suggested phosphate buffer solution is prepared so that it has a tonicity equivalent to a 0.9 per cent sodium chloride solution, therapeutic amounts of all the drugs recommended for use in it can be added without exceeding an acceptable limit of tonicity. We have set this limit at a 1.4 per cent sodium chloride equivalent, since this is the higher value given for the tonicity of the tears and is safely below the level of a 2.0 per cent equivalent, which is the point where damage to

TABLE 4.—p_H of Various Commercial Products

p_H	Product	Solution		
		Hypotonic	Isotonic	Hypertonic
7.36	Antistine *	..	†	..
6.4	Equal parts of naphazoline hydrochloride (privine) 0.05% and antistine *	..	†	..
5.5	Neostigmine hydrobromide, 5.0%	..	†	..
5.39	Phenylephrine (neosynephrine) § hydrochloride, 1.25%	..	†	..
7.55	Phenylephrine hydrochloride, 2.5% (ascorbic acid buffer)	..	†	..
5.50	Phenylephrine hydrochloride, 2.5% (citrate buffer)	..	†	..
5.07	Phenylephrine hydrochloride, 10%	..	..	†
5.36	Paredrine § hydrobromide ‡	..	†	..
5.2	Butacaine sulfate, 2.0%	..	†	..
†4.19	Tetracaine (pontocaine §), 0.5%	†	..	..

* Trademark for 2-phenylbenzylaminomethyl-imidazoline.
† p_H 5.0 when prepared in isotonic sodium chloride solution with 1:5,000 benzalkonium chloride.
‡ A 1 per cent solution of p-hydroxy-α-methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2% boric acid and preserved in merthiolate, 1:50,000.
§ Registered trademark.

the corneal epithelium probably begins. A table of the maximum amounts (table 5) of the drugs to be used in this solution is presented. Any amount below the values given is, of course, satisfactory. The values in the "safe maximum amount" column are expressed in easily remembered percentages by weight for facility in using and remembering the figures given in the table, while being close enough to the theoretic value for safety (table 5).

One of the most commonly used ophthalmic therapeutic solutions is one containing zinc sulfate. Lipschütz,[3] in the same article in which he published his results and conclusions regarding the relation of the p_H to the sensation a solution produces, also stated reasons that he believed zinc sulfate should be dispensed in a definitely acid solution. At the same time, no one wishes to dispense a solution about which a patient

will complain. For this reason, efforts have been made to find ways of buffering zinc sulfate solutions to more neutral p_H values while obtaining a solution which was also chemically stable.

The most frequently used vehicle for zinc sulfate is a boric acid solution. We tested 12 volunteer resident physicians with a 2 per cent solution of boric acid containing 0.032 Gm. of zinc sulfate (0.1 per cent) to the ounce. (It will be noted above that 100 per cent of those tested in a similar group with a 2 per cent solution of boric acid found the solution nonirritating.) One complained of a slightly uncomfortable feeling, like "a foreign body," which passed in about two minutes. One complained of a "peculiar dry feeling," which was transitory. Two complained of a definite, but slight, transitory burning sensation. Nothing alarming was experienced by any of the volunteers; even the

TABLE 5.—*Percentage of Drugs (W/V) Which Should Not Be Exceeded When Drug is Used in Recommended Phosphate Buffer Unless a Hypertonic Solution is Desired**

Drug	Molecular Weight	Calculated △ C. for a 1% Solution	Factor for Ionization	Theoretic Maximum Amount, %	Safe Maximum Amount, %
Atropine sulfate (with 1 molecule water of crystallization)	694.82	—0.08	3	3	3
† Homatropine hydrobromide	352.26	—0.105	2	2.5	2.5
† Eucatropine hydrochloride	327.84	—0.113	2	2.1	2.5
Scopolamine hydrobromide	384.27	—0.094	2	2.6	1.0‡
Pilocarpine hydrochloride	244.73	—0.15	2	1.6	2.0
Ephedrine sulfate	428.53	—0.13	3	1.8	2.0

* Complete ionization is assumed.

† Five per cent solutions of this drug with a tonicity that is theoretically almost exactly that desired may be made by omitting the sodium chloride from the phosphate buffer formula given.

Formula (Remington, J.: Practice of Pharmacy, ed. 8, revised by E. F. Cook, C. N. LaWall and others, Philadelphia, J. B. Lippincott Company, 1936, pp. 198-200): The decrees (Centigrade) that a substance will lower the freezing point of 100 cc. distilled water equals

$$\frac{-1.86 \times \text{factor for ionization}}{\frac{\text{Molecular weight}}{10}}$$

—0.56 C. is the △ C. of the buffer solution; —0.80 C. is the maximum theoretically desirable limit. Hence, the theoretic maximum amount given above is found by dividing 0.24 by the calculated △ C. of the drug for a 1% solution.

The "safe amount" is that amount which will not exceed the tonicity of a solution having a △ C. of —0.80 C., and an amount which is easily remembered for facility in application of the table. The tonicity of solutions containing these amounts of drug is safely less than that amount which will produce damage to the epithelium of the excised cornea experimentally.

‡ There is probably no therapeutic reason for exceeding this amount, as stronger solutions are too likely to produce systemic reactions.

two who complained of burning stated that it "did not amount to much." Our findings with use of the solutions of Arrigoni, Fischer and Tozer [4] are given in table 2. The absence of any need for a zinc sulfate solution to have a value approaching neutrality is shown, we believe, as well as the importance of the chemical constituents of a solution in relation to the sensation the solution will produce.

Even if a few persons do experience a transitory, mild unpleasantness with zinc sulfate solutions, unless the solution is to be dispensed for purely psychologic reasons, an acid one is to be preferred. The Morax-Axenfeld bacillus, as well as other organisms, does not grow at a p_H of less than 7.[11] Since the corneal epithelium is not harmed by p_H values above 4.5, certainly an acid solution of zinc sulfate would be therapeutically desirable. We found that mixing 17.5 cc of Arrigoni, Fischer and Tozer's acid solution with 12.5 cc of their alkaline solution will give a solution of p_H 6.65, which may be used if one prefers their buffer.

It is frequent practice to add epinephrine to zinc sulfate solutions. We found that the epinephrine in these solutions was unstable. The epinephrine breaks down readily in such dilute solutions. We suggest that, when a decongesting vasoconstrictor is needed 0.015 to 0.030 Gm. (0.05 to 0.1 per cent) of ephedrine sulfate per 30 cc be added. This drug is slightly slower acting but is equally effective and is longer acting, without undesirable side effects, in this strength, and is stable in solution at this concentration. Zinc sulfate is incompatible with borates, and we noted that all solutions containing only zinc sulfate and 2 per cent boric acid form a fine, powdery precipitate on long standing. Glycerin was tried as a stabilizer for the solution and found to be effective. Some type of boroglycerate complex may be formed. A zinc sulfate vehicle with the glycerin in slight stoechiometric excess over the boric acid should be stable and allow the zinc ion full therapeutic effectiveness. Such a solution is presented in table 6. To this vehicle may be added the desired amount of zinc sulfate and, if desired, a decongesting agent, such as ephedrine or epinephrine. This preparation has been used several times weekly for several months by one of us (J. L. M.), has been found not unpleasant to use and has produced no deleterious effects. It has also been prescribed for numerous patients, who volunteered no complaints in regard to the solution.

The benzalkonium chloride used in this solution is compatible with boric acid in the amount used. These two substances are not incompatible except in solutions in which boric acid is in a concentration approaching saturation.

Hind and Goyan recommended the use of metabisulfite to stabilize physostigmine in solution. We found that plain sodium bisulfite was more generally available and equally effective. Good precedent exists for its use, as it is the substance used to stabilize many of the commercially available epinephrine solutions which are widely used in ocular therapy. We prepared the physostigmine solution by this formula and placed it in two white glass containers. Both were still clear and white

11. Zinsser, H.: Zinsser's Textbook of Bacteriology, ed. 9, revised by David T. Smith and others, New York, D. Appleton-Century-Croft Company, Inc., 1948, p. 328.

after five months, in spite of the fact that the tops were left loose and the solutions agitated at frequent intervals. While it is stated that physostigmine solution which has turned red is still active, certainly

TABLE 6.—*Suggested Ophthalmic Solutions*

I. Cocaine hydrochloride, 5% containing 1% sodium lactate (anhydrous)	
II. Zinc sulfate vehicle (add amount of zinc sulfate desired)	
Boric acid	0.86 Gm.
Glycerin U. S. P.	1.32 cc.
Benzalkonium chloride 1:1,000	3.00 cc.
Distilled water to	100.00 cc.
or	
Boric acid	0.200 Gm. (gr. 5)
Glycerin U. S. P.	0.440 cc. (min. 7)
Benzalkonium chloride 1:1,000	1.000 cc. (min. 15)
Distilled water	30.000 cc. (oz. 1)
III. Physostigmine	
Physostigmine salicylate	0.250 (0.25%)
Sodium bisulfite	0.300
Boric acid	2.000 Gm.
Distilled water	100.000 cc.
or	
Physostigmine salicylate, 0.500 (0.5%)	0.092 Gm. (1½ gr.)
Sodium bisulfite	0.060 Gm. (1 gr.)
Boric acid	0.65 Gm. (10 gr.)
Distilled water	30.00 cc. (1 oz.)
IV. Tetracaine hydrochloride (pontocaine *)	
Tetracaine hydrochloride	0.250 Gm.
Benzalkonium chloride 1:1,000	30.000 cc.
Isotonic sodium chloride solution qs ad	100.00 cc.
V. Phosphate buffer solution for atropine sulfate, homatropine hydrobromide, eucatropine hydrochloride, scopolamine hydrobromide, pilocarpine hydrochloride † and ephedrine sulfate.	
Sodium biphosphate U. S. P. (anhydrous) ‡	4.000 Gm.
Sodium phosphate U. S. P. (anhydrous)	4.730 Gm.
Sodium chloride	4.300 Gm.
Benzalkonium chloride 1:1,000 sol. §	30.000 cc.
Distilled water	1,000.00 cc.
or	
Sodium biphosphate U. S. P. (anhydrous)	0.132 Gm.
Sodium phosphate U. S. P. (anhydrous)	0.156 Gm.
Sodium chloride	0.142 Gm.
Benzalkonium chloride 1:1,000	1.000 cc.
Distilled water qs ad	30.00 cc.

* Registered trademark.

† Pilocarpine nitrate should not be used.

‡ Neither sodium acid phosphate or disodium phosphate is available readily or economically in anhydrous form. Allowance must always be made in preparing this solution for the water of crystallization in the salts being used.

§ Apparently, benzalkonium chloride may be added to this solution up to 20.00 cc. of the 1:1,000 solution, per 100 cc. of solution, thus producing bacteriologically a "self-sterilizing solution" (McPherson, S. D., and Wood, R. M.: Self-Sterilizing Ophthalmic Solutions, Am. J. Ophth. **32**:675 [May] 1949). All our investigations were carried out, however, with the formula given before the article referred to was published. The solution given above is stable and remained free from mold growth, although some solutions were given every opportunity for contamination with molds.

a more stable solution would be superior, probably less irritating and therapeutically more effective.

When we prepared a solution containing 4 per cent cocaine hydrochloride and 2 per cent boric acid, as Hind and Goyan [9] suggested, we obtained a solution of p_H 3.8. We did not test more than one preparation of this solution. We attempted to buffer cocaine hydrochloride to a higher p_H either in the phosphate buffer or in a borate buffer. The solution was not stable more than a few hours in any preparation we tried in which the p_H of the solution was above 6. We found that adding sodium lactate to a solution of cocaine hydrochloride in the ratio of 3 parts to cocaine hydrochloride to 1 part of sodium lactate produced a solution that had a p_H varying from 5.05 to 5.10. This solution is apparently stable for at least two weeks. We feel that any cocaine solution should be made up fresh each week. No preservative is necessary for this reason; moreover, cocaine itself is mildly antiseptic. If the solution contains 3 per cent of cocaine hydrochloride and 1 per cent of sodium lactate, it will be in the range of acceptable tonicity.

Tetracaine hydrochloride requires no buffering and is probably best prepared in isotonic sodium chloride solution. We feel that its action is enhanced by adding 1:5,000 benzalkonium chloride as a preservative, since its detergent action increases corneal permeability to the drug. The commercial 0.5 per cent solution was found by us to have a p_H of 4.19. The solution we recommend had a p_H of 5.2 (table 4).

Chlorobutanol and pentobarbital have been shown by Herrmann, Moses and Friedenwald [12] to inhibit the oxygen uptake of the cornea. Because many of the therapeutic agents that must be used in the eye do the same thing, it would seem unwise to use these compounds for any other than therapeutic reasons in ophthalmic solutions. They should not be used as preservative or buffer.

Hosford and Hicks [13] stated that the kind of glass out of which a bottle is made and the kind of liquid with which it is rinsed before use are among the most important factors concerned in the immediate sensation produced when a therapeutic solution is instilled into the conjunctival sac. We avoided the possibility of this influence by careful choice of and rinsing of the glassware we used in our experiments on the relation of the p_H of various solutions to the sensations they produce. We did not run any tests to determine the validity and importance of these two factors. We assumed that they were of some importance and attempted to eliminate them as much as possible. If glass bottles of a

12. Herrmann, H.; Moses, S. G., and Friedenwald, J. S.: Influence of Pontocaine Hydrochloride and Chlorobutanol on Respiration and Glycolysis of the Cornea, Arch. Ophth. **28**:652-660 (Oct.) 1942.

13. Hosford, G. N., and Hicks, A. M.: Hydrogen Ion Concentration of Tears: Its Relation to Certain Ocular Symptoms and to Conjunctival and Corneal Lesions, Arch. Ophth. **13**:14-25 (Jan.) 1935.

good grade are used in dispensing and the bottles are rinsed with 0.1 normal hydrochloric acid, drained, again rinsed with distilled water and allowed to drain dry upside down shortly before they are used for dispensing, they should not be a source of trouble. If a screw cap bottle is used, as is advisable, the type of seal in the cap is also a matter of importance.

In considering the tonicity of a solution of a salt of any alkaloid, the acid ion must be known specifically and carefully considered. Also, this portion of the molecule must always be remembered when a question of compatibility arises. Frequently, published data leave the reader very much in doubt as to whether certain statements apply to an alkaloid as its insoluble base or to a salt the acid radical of which is not stated. Prescriptions should always state which acid salt is desired when a soluble salt of an alkaloid is prescribed.

SUMMARY

1. Any solution to be instilled into the conjunctival sac which has a tonicity equivalent between that of a 0.9 and a 1.4 per cent solution of sodium chloride is acceptable. More accurate adjustment for tonicity than this is not necessary.

2. Any solution to be instilled into the conjunctival sac should have a p_H of 4.5 to 9. If the factor of the sensation produced must be ignored for chemical, pharmaceutical or therapeutic reasons, any solution having a hydrogen ion concentration between these limits is acceptable as far as the integrity and healing of the cornea are concerned.

3. Isotonic phosphate buffer solutions do not produce any unpleasant sensation in the majority of eyes when instilled into the conjunctival sac if the p_H of the solution is between 6.6 and 8.7. There is, however, no justification for assuming that isotonic solutions of other chemical composition having hydrogen ion concentrations outside these limits will prove irritating. Whether or not a particular p_H value of a solution will prove of itself to be a source of irritation must be determined for any given combination of ions and substances in solution. Experimental evidence for this statement is presented.

4. The importance of the chemical stability of a drug in solution as dispensed to a patient is pointed out, and a phosphate buffer is presented which represents at present the best compromise of the several factors concerned. This solution is intended as a vehicle for those drugs not commonly dispensed as commercially prepared solutions and for drugs which will remain stable if buffered near the neutral point. A table is presented of the amounts of each drug which may be used in these vehicles without exceeding the upper limits of acceptable tonicity.

5. The majority of drugs which require a lower hydrogen ion concentration for stability in solution are usually dispensed as commercially compounded solutions. Some of those frequently used were tested, and most were found to have an acceptable p_H value. Most such solutions were also calculated on the basis of their published formulations to have an acceptable tonicity (table 4).

6. A stable, therapeutically acceptable vehicle for zinc sulfate is presented. The advantages of ephedrine over epinephrine as a component of such solutions is pointed out.

7. Vehicles are described for physostigmine, zinc sulfate, cocaine hydrochloride and tetracaine hydrochloride which we believe to be the most acceptable at present.

HUMAN INFECTION WITH THE NEWCASTLE VIRUS OF FOWLS

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NEWCASTLE disease, or avian pneumoencephalitis, is a highly communicable virus disease of fowls, which was first recognized as an entity in the Netherlands East Indies in 1926.[1] Within the next few years scattered reports were issued from various parts of the Orient and Australia identifying similar disease processes in fowls and reporting them under colloquial or indigenous names.[2] Doyle,[3] in 1927 at Newcastle-on-Tyne, England, clearly established the etiology and nature of the malady during an outbreak in the chicken flocks of that area. The avian disease is usually characterized by a sudden appearance of respiratory signs, followed by neurologic disturbances, which, outside the United States, have led to a mortality of about 90 per cent.

Newcastle disease in fowls was first recognized in America about 1941 [4] and subsequently has been identified in all of the states of the Union [5] and most of the provinces of Canada, as well as in many European and African areas. In the United States poultry mortality from this disease has averaged 30 per cent. Chickens and turkeys are particularly susceptible, and other common fowl have been known to become infected.

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1. Kraneveld, F. C.: Over een in Ned.-Indie heerschende ziekte onder het pluimvee, Nederl.-indische bladen v. diergeneesk. **38**:448-450, 1926.

2. Beaudette, F. R.: Review of the Literature on Newcastle Disease, Proc. Forty-Seventh Annual Meeting of the United States Live Stock Sanitation Association, December 1943, pp. 122-177.

3. Doyle, T. M.: A Hitherto Unrecorded Disease of Fowls Due to a Filter-Passing Virus, J. Comp. Path. & Therap. **40**:144-169 (June) 1927.

4. Beach, J. R.: Avian Pneumoencephalitis—Past and Present, Nulaid News **23**:26-29, 1946.

5. Thompson, C. H.: Newcastle Disease, Mil. Surgeon **106**:276-281 (April) 1950.

Diseased animals discharge the virus in their oral and nasal secretions and also in their feces.[6] Recovery of the virus from the blood of infected fowls has only occasionally been successful. The eggs of affected parent stock have been shown [7] to contain the virus, and they constitute another potential source of human infection. The disease has been alleged to spread between chicken flocks through the medium of reused feed bags, unclean crates and even human visitors.[8] In the past few years this virus has become a major problem in one of the commonest food sources.

The infection can be transmitted to humans, but no cases had been recorded in the United States prior to four which occurred in 1948; (Freymann and Bang [9]; Ingalls and Mahoney [10]). It is not unlikely, however, that other cases of the infection have occurred. In no report

TABLE 1.—*Clinically Identified Newcastle Infections in Humans*

Author	Cases	Case No.	Virus Found	Place	Date	General Symptoms	Antibody Response	Incubation	Preauricular Node	Bacterial Study
Burnet [11a]	1	..	Yes	Australia	1943	Malaise; chills; headache	Slight	?	Yes	....
Yatom [11b]	17	..	....	Israel	1946	?	?	About 3 days	?	....
Anderson [11c]	2	1	Yes	Australia	1946	None	None	2 days	No	....
	..	2	Yes	Australia	1946	?	None	?	Yes	....
Shimkin [11d]	1	..	....	Ha./a	1946	None	?	1 day	?	Yes
Rachmel [11e]	4	1	....	Budapest	1947	Malaise; fever	?	1 day ?	Yes	Yes
	..	2	....	Budapest	1947	Fever	?	1 day ?	Yes	Yes
	..	3 and 4	....	Budapest	1947	Fever	?	?	Yes	....
Freymann and Bang [9]	3	1	Yes	Baltimore	1948	None	Slight	1 day	Yes	....
	..	2	Yes	Baltimore	1948	None	Slight	1 day	Yes	Yes
	..	3	....	Baltimore	1948	None	Slight	?	Yes	....
Ingalls and Mahoney [10]	2	1	Yes	Ohio	1948	None	Strong	Under 3 days	?	....
	..	2	Yes	Ohio	1948	None	?	1 to 2 days	?	....
Beaudette [12]	3	1	....	New Jersey	1930	?	?	Under 3 days	?	....
	..	2	....	New Jersey	1930	?	?	?	?	....
Kenney and Hunter	1	..	Yes	Philadelphia	1950	Chills; fever; back and headache	Strong	About 18 hr.	Yes	Yes

has the disease been noted to spread from one human to another. The manifestations of Newcastle infection in humans have, thus far, been confined to an acute granular conjunctivitis, often with preauricular adenitis and sometimes with fever, headache, chills and malaise. Secretions are scarce, and corneal involvement has not previously been

6. Bushnell, L. D., and Erwin, L. E.: Distribution of Newcastle Virus in Tissues of Chickens, Tr. Kansas Acad. Sc. **52**:373-374, 1949.

7. Delay, P. D.: Isolation of Newcastle Virus from Chicks, Embryos, and Infertile Eggs, Science **106**:545-546 (Dec. 5) 1947.

8. Hall, W. J.: Diseases and Parasites of Poultry, Farmer's Bulletin no. 1652, United States Department of Agriculture, March 1949, pp. 33-35.

9. Freymann, M. W., and Bang, F. B.: Human Conjunctivitis Due to Newcastle Virus, Bull. Johns Hopkins Hosp. **84**:409-413 (May) 1949.

10. Ingalls, W. L., and Mahoney, A.: Isolation of Newcastle Virus from Humans, Am. J. Pub. Health **39**:737-740 (June) 1949.

described. To date, there have been seven published reports,[11] covering 30 clinical cases which fall into the picture of human Newcastle disease. In each case there has been direct contact with sick poultry or known strains of the Newcastle virus. Incubation periods of a few hours to about two days have been reported, and all patients have recovered in five days to two weeks without sequelae.

Parenthetically, it is to be noted that at least two reports have been published linking human encephalitis [12] and gastroenteritis [13] with the Newcastle virus. These reports were based on the demonstration of nonspecific, heat-labile factors rather than on a specific Newcastle virus antibody response in convalescent serum. Correction of this work by Howitt has recently been published.[14]

The 30 reported cases, plus two recently under investigation at Rutgers University,[15] and the case reported in this paper show the following occupational distribution:

Laboratory workers	9
Kitchen personnel	19
Poultry feed salesman	1
Broiler plant operator	1
Veterinary student	1
Unknown	2
Total	33

Unfortunately, the clinical, virologic and immunologic aspects of this disease have been incompletely described in most reports of human cases. In only four [16] reports, covering seven cases, have there been recovery and identification of the virus from the conjunctiva; in only one [9] of these cases has an attempt been made to rule out concurrent bacterial infection which might have been responsible for the clinical picture. Immune

11. (*a*) Burnet, F. M.: Human Infection with the Virus of Newcastle Disease, M. J. Australia **2**:313-314 (Oct. 16) 1943. (*b*) Yatom, J.: An Outbreak of Conjunctivitis in Man Associated with the Newcastle Virus, Harefuah **30**:58 (Feb. 1) 1946. (*c*) Anderson, S. G.: Two Laboratory Infections with the Newcastle Virus, M. J. Australia **1**:371 (March 16) 1946. (*d*) Shimkin, N. I.: Conjunctival Hemorrhage Due to Newcastle Virus Infection in Man, Brit. J. Ophth. **30**:260-264 (May) 1946. (*e*) Radnot, M.: Maladie oculo-glandulaire jusqu'à présent inconnue, Ophthalmologica **113**:106-107 (Feb.) 1947. (*f*) Freymann and Bang.[9] (*g*) Ingalls and Mahoney.[10]

12. Howitt, B., and others: Neutralizing Antibodies to Newcastle Disease in Human Sera, Am. J. Pub. Health **38**:1263-1272 (Sept.) 1948.

13. McGough, T. F.: Outbreak of Newcastle Disease in Ohio, Ohio State M. J. **45**:25-26 (Jan.) 1949.

14. Howitt, B.: Nonspecific Factors in Serum Neutralization Test for Newcastle Disease, J. Immunol. **64**:73-84 (Feb.) 1950.

15. Beaudette, F. R.: Personal communication to the authors.

16. Burnet,[11a] Anderson,[11c] Freymann and Bang,[9] Ingalls and Mahoney.[10]

responses were studied serologically in six of the seven cases in which the virus was recovered, but in only three was there a definite rise in antibody titer. In none of the previously reported cases has the virus been recovered from the blood stream.

Thus, from 30 clinically identified cases of an apparently new human disease, only one appears in the literature with ample data to withstand critical analysis. It is our purpose to report a proved case of human Newcastle disease with more extensive corroborating data and to present certain details of the disease not previously described.

REPORT OF A CASE

On Jan. 19, 1950, at 11:00 a. m., one of us (M. C. H.) became infected with the virus. An embryonated chick egg inoculated 48 hours previously with a known strain (Beaudette no. 2) of Newcastle virus was accidentally crushed and the material splashed over the patient's face, arms and chest. He immediately washed his face and hands several times, autoclaved his clothing and scrubbed under a hot shower. His eyes were rinsed many times in the shower and during the rest of the day irrigated hourly with boric acid solution. No reaction was observed until the following morning, when the conjunctiva was found to be quite red but without discomfort. At 10:00 a. m. he was seen by Dr. Bernard C. Gettes, through whose courtesy the clinical studies have been conducted at Wills Hospital.

On examination (January 20), there was a trace of edema of the lids, and the conjunctiva appeared granular (++) and congested (+++), owing to papillary hypertrophy. The involvement was greater in the inferior than in the superior fornices. The bulbar conjunctiva was moderately injected. Only scant secretions, with no pus or mucus shreds, were present. The corneas were free of infiltrates and did not stain with fluorescein. The anterior chambers were optically empty. Conjunctival smears showed many lymphocytes, few segmented granulocytes and no bacteria. No bacterial colonies could be detected on blood agar slants inoculated with conjunctival material from each eye.

Late in the afternoon there developed headache, backache and fever, the temperature gradually increasing to 100.2 F. At 1:00 a. m. (January 21) he was awakened with a shaking chill, which lasted 30 minutes and was accompanied with epiphora. He again fell asleep until 8:00 a. m. On his awakening, the lids were crusted together with dried secretions, and the temperature was 98 F. He had a greenish, fluid bowel movement.

On the second day (January 21), conjunctival hyperemia was still about the same, but a few pinpoint epithelial infiltrates were present in each cornea, and two or three took a light fluorescein stain. Vision, which had been 6/6 in the right and left eyes the previous morning, dropped to 6/6-3 and 6/9, respectively. Blood agar cultures of material from each eye again yielded no growth. The patient remained comfortable that day and night.

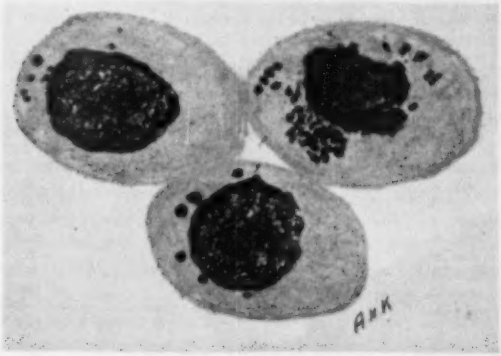
On the third day (January 22), both eyes continued to itch and water somewhat, but there was a reduction in conjunctival hyperemia and papillary hypertrophy. The epithelial infiltrates were about the same; but staining remained only in the left cornea, and vision had improved several letters. The upper cul-de-sacs showed about half the amount of capillary dilatation and petechiae present in the lower.

On the fourth day (January 23) excess secretions had subsided almost entirely. However, a preauricular lymph node, about 5 mm. in diameter, on the left side

became palpable and was tender for three days. There was notably less bulbar injection and no corneal staining.

During the next two weeks the injection and pebbly roughness of the conjunctiva gradually subsided—most rapidly in the bulbar portions, least rapidly in the inferior fornices. Symptoms of stickiness on awakening and dryness during the day regressed *pari passu*. By the tenth day (January 30) both corneas were clear and vision was normal. Two weeks after onset of symptoms the patient felt well, but a dusky hyperemia remained in the lower fornices for another ten days.

On the second and fifth days of infection, scrapings were made from the lower cul-de-sacs, and small granular, cytoplasmic inclusions, varying in color from Burgundy to dark bluish purple, were demonstrated in the epithelial cells of the conjunctiva with Giemsa stain (after fixation in absolute alcohol). Scrapings made on the seventeenth day (February 7) revealed entirely normal epithelial cells. Attempts to reproduce this cell picture in conjunctival scrapings from rabbit eyes



Cytoplasmic inclusions in the epithelial cells of the conjunctiva, as demonstrated in scrapings made during the first week following infection with Newcastle virus (drawing from Giemsa stain).

inoculated with Newcastle virus and in meningeal and chorioallantoic membrane scrapings from infected chick embryos have been unsuccessful.

The systemic pattern of Newcastle disease is reflected in both the white blood cell count and the serum antibody response. On the second day of infection (January 21) there was leukopenia, with a count of 5,850 and a relative lymphocytosis of 42 per cent (segmented granulocytes, 52 per cent). The leukocyte count returned to 9,500 on the sixth day (January 25), where it has remained. The lymphocyte count, however, showed no significant drop during the next two weeks but by February 28 had fallen to 33 per cent.

Treatment.—In accordance with the survey of Braley,[17] in which aureomycin was found effective against the virus of inclusion conjunctivitis, and also in cases of acute follicular conjunctivitis of unknown origin but resembling the Béal type, it was decided to attempt treatment with 0.5 per cent aureomycin borate drops

17. Braley, A. E., and Sanders, M.: Aureomycin in Ocular Infections, Am. J. Ophth. **32**(pt. 2):119-127 (June) 1949.

instilled hourly in the right eye. Experimentally, penicillin drops (5,000 units per cubic centimeter) were instilled hourly in the other eye. These medications were instituted on the first day of illness but were discontinued with subsidence of major symptoms on the fourth day (January 23). There was no indication that either had influenced the infection, and active virus was recovered from both eyes after this treatment.

Because of persistent dryness and stickiness nine days after infection, a zinc sulfate solution was prescribed (January 28) for use in one eye only. This had no effect, as compared with the other eye. Cunningham,[18] from a study of the in vitro sensitivity of this virus to many agents, reported that tincture of benzalkonium (zephiran®) chloride (1:1,000) or benzethonium chloride, 3 per cent, will kill the virus in three minutes, but these agents are not suitable for conjunctival instillation.

VIROLOGY

The Newcastle virus is a medium-sized virus and differs from most other animal viruses in being spermlike in shape when suspended

TABLE 2.—*Leukocyte Response Following Infection with Newcastle Virus*

Date	Total Leukocyte Count	Lymphocytes %
Jan. 19	Patient infected with Newcastle virus	
Jan. 21	5,850	42
Jan. 23	6,750	45
Jan. 25	9,300	45
Jan. 27	9,300	44
Jan. 30	.....	44
Feb. 2	9,000	47
Feb. 28	9,200	38

in saline solution.[19] The head is about 70 millimicrons wide and 180 millimicrons long and bears a tail as long as 500 millimicrons. The virus multiplies readily in embryonated chick eggs,[20] and allantoic fluid from infected embryos is capable of agglutinating erythrocytes from humans and a number of other animal species.[21]

Antibodies produced as a result of Newcastle infection have usually been demonstrated by the hemagglutination inhibition method, but several other immunologic tests are available.

18. Cunningham, C.: Effects of Chemical Agents on Newcastle Virus, Am. J. Vet. Research **9**:220-224 (April) 1948.

19. Bang, F. G.: Filamentous Forms of Newcastle Virus, Proc. Soc. Exper. Biol. & Med. **63**:5-7, 1946. Cunha, R., and others: Characteristics of the Newcastle Virus, J. Immunol. **55**:69-89, 1947.

20. Bushnell, L. D., and Erwin, L. E.: Increase of Newcastle Virus in Embryos, Tr. Kansas Acad. Sc. **53**:66-67, 1950. Burnet, F., and Ferry, J.: Viruses of Fowl Plague and Newcastle Disease, Brit. J. Exper. Path. **15**:56-64, 1943.

21. Burnet, F.: Affinity of Newcastle Virus to the Influenza Group, Australian, J. Exper. Biol. & M. Sc. **20**:81-88, 1942.

The disease in humans is diagnosed on a history of exposure, isolation of the virus, demonstration of a significant immune response and exclusion of bacterial pathogens.

In this case the virus was recovered from embryonated chick eggs inoculated with conjunctival washings. Second and third passages of the virus material from the allantoic fluid of the originally inoculated eggs were carried out for verification. Increasing hemagglutination titers were found in each subsequent passage. A transient viremia was also demonstrated, and a significant rise in hemagglutination inhibition titer of the patient's serum (heat inactivated) was found a week after the infection. A detailed account of the related virology and a long term study of the immune response are in preparation.

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of Newcastle disease, two groups of conjunctival inflammations should be considered:

A. Acute catarrhal conjunctivitis, such as that due to Diplococcus pneumoniae, Staphylococcus aureus, Koch-Weeks bacillus or Hemophilus influenzae.

The initial symptoms here may be quite similar to those of Newcastle disease, but systemic signs are absent and the discharge is more profuse and mucopurulent. Smears or scrapings will show the preponderance of neutrophilic granulocytes and usually the causative bacteria.

B. Acute follicular conjunctivitis, such as the inclusion conjunctivitis of adults, Béal's conjunctivitis and epidemic keratoconjunctivitis.

These diseases are more truly follicular in that the subepithelium shows a lymphocytic response, whereas in Newcastle disease a papillary or primary vascular response is more pronounced.

(*a*) In Béal's conjunctivitis the scanty secretions and similar course are confusing, but the usually intense concentration of follicles and complete sparing of the cornea aid in diagnosis. No virus has been recovered in cases of this disease, nor has Thygeson [22] been able to transmit the disease to common laboratory animals.

(*b*) In inclusion conjunctivitis of adults (swimming pool conjunctivitis, or paratrachoma) cytoplasmic inclusions might be confused with those demonstrated in the present case, but the symptoms are usually severer. The discharge is purulent and loaded with segmented granulocytes. Both the acute and the convalescent phase run a much longer course than that in Newcastle disease.

(*c*) In epidemic (shipyard) keratoconjunctivitis secretions are scanty and the onset is similar to Newcastle disease, but the development

22. Thygeson, P.: Viruses and Virus Diseases of the Eye: II. Viruses of Ocular Importance (Concluded), Arch. Ophth. **29**:635-661 (April) 1943.

of a pseudomembrane, intranuclear inclusion bodies, more pronounced corneal infiltrates and visual impairment soon make the diagnosis clear.

Some of the many cases that have been classified under the morphologic diagnosis of superficial punctate keratitis may actually have been instances of Newcastle virus infection. Similarly, the disease described by Patton and Gifford [23] (1921) as agricultural conjunctivitis in farming districts of America may have been this infection from diseased fowls in some cases.

SUMMARY

We present a proved case of Newcastle infection in man and indicate the nature of the avian disease and its place of increasing significance in our food supply. The disease in man appears much less severe than it may be in fowls and is primarily marked by acute papillary conjunctivitis with regional lymphadenitis and secondary infiltration of the corneal epithelium. Cytoplasmic changes in the epithelial cells which appear to be inclusion bodies were demonstrated in the early course of the illness. Since these bodies are a new finding in Newcastle disease in either the natural host or the human, definite proof that they are virus inclusions rests on subsequent demonstration of such particles in experimentally induced infection. Systemic symptoms of mild leukopenia, relative lymphocytosis, headache and chills occurred as brief phenomena associated with a transient viremia. Bacterial infection was excluded, and virus material isolated from the conjunctiva and the blood stream was identified as Newcastle virus. A significant antibody response was demonstrated in the patient's serum.

23. Patton, J. M., and Gifford, R. G.: Agricultural Conjunctivitis, Tr. Sect. Ophth., A. M. A. **27**:226-256, 1921.

Clinical Notes

LARGE SIZE COLOR TRANSPARENCIES OF PATHOLOGIC SLIDES

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NEW YORK

LARGE size color transparencies of pathologic sections are well known to every lecturer and demonstrator. Heretofore the making of such transparencies has been a difficult and costly process. The following method developed at the New York Eye and Ear Infirmary has proved highly successful and can be utilized by the average photographer with little more than standard photographic equipment.

The following equipment has been used successfully to provide accurate color transparencies (3¼ by 4¼ inches [8.3 by 10.8 cm.]) with excellent color rendition:

1. Camera. A standard 5 by 7 inch (10 by 17.8 cm.) view camera with a reducing back. (Any camera with bellows extension may be used.)

2. Tripod. A sturdy tripod is an essential factor, as exposures will usually be longer than ½ second.

3. Film. Ektachrome* daylight film is used and processed according to the manufacturer's recommendation (at 68 F.). However, if richer colors are desired, the photographer may decrease the exposure one-half stop and develop the film for 20 minutes in the first developer, instead of the recommended 15 minutes.

4. Light source. This is the most important item of all. The light source used is a cold light grid [1] with a 4500° (Kelvin) grid (fig. 1). A wooden adapter is placed over the grid light assembly with an aperture 2 inches (5 cm.) in diameter, situated 3½ inches (8.9 cm.) from the top of the grid (fig. 2).

To use this technic the pathological slide to be photographed is secured with scotch tape across the center of the 2 inch aperture. If it is desired, one may construct a holder for such a purpose. A piece of opal glass is placed over the top of the grid, and the assembly is enclosed in the adapter. The entire mechanism is then placed on a firm table, and the camera is focused on the section to be photographed. From this point in the procedure the photographer may rely on his own experience. Exposure should be determined by test. However, it may be of some help to know that with a 6 inch (15 cm.) lens, an aperture of f4.7 and a 24 inch (60 cm.) bellows extension the exposure was found to be one second.

In making exposures of more than ½ second with a large bellows extension, it is advisable to observe the following procedure: After focusing, securely lock the camera in position and close the shutter.

From the Department of Photography, New York Eye and Ear Infirmary.

1. Cold grid lite,* manufactured by the Aristo Grid Lamp Prod., Inc.

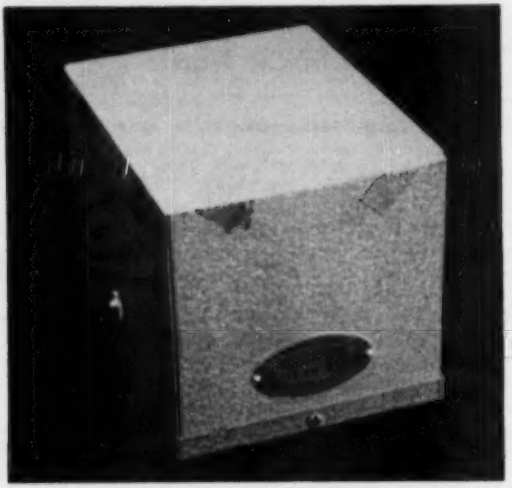

Fig. 1.—Cold light grid. Note the opal glass attached with scotch tape.

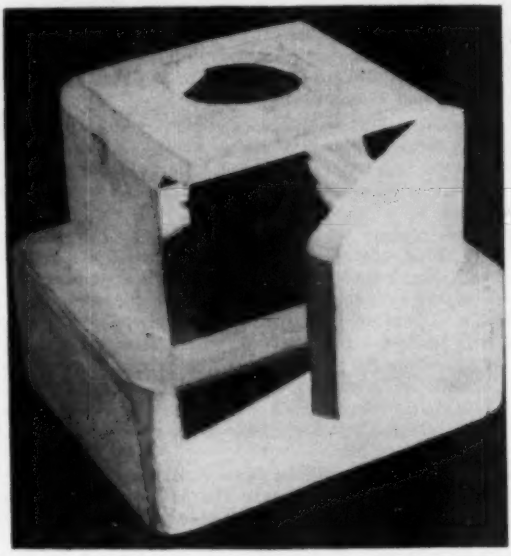

Fig. 2.—The wooden adapter. Note the hinged side and slots for insertion of filters or diffusion glass.

Gently place the filmholder in position in the camera back and remove the dark slide. Hold the dark slide in front of the lens, so that no light falls on the film. Open the shutter (using "Time"). Wait a moment until the camera settles itself. Now remove the dark slide for the exposure time required. After the exposure, replace the dark slide in front of the lens. Close the shutter. Insert the dark slide in the film holder and remove the holder.

Basically, the entire technic is simple but is capable of accurate reproduction.

When possible, a cold grid light which has burned at least 100 hours should be used. This "aged" grid light should be allowed to burn an hour before making the first exposure. A light so treated will not be affected by fluctuations in voltage and will give a constant color correction. The grid light should be kept burning at all times when one is working.

Ektachrome® film has a tendency to lose its latent image and should be processed as soon as possible, preferably the same day as that of the exposure.

SUMMARY

The production of large size color transparencies is ordinarily a difficult and costly process. A technic, developed at the New York Eye and Ear Infirmary, which is simple and economical and which can be employed by the average photographer, is presented.

218 Second Avenue (3).

Annual Reviews

PHYSIOLOGIC CHEMISTRY OF THE EYE

A Review of Papers Published During 1949

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BOSTON

PHYSIOLOGIC chemistry deals with the chemical processes that take place in an organism. The elucidation of these processes depends on knowledge of various factors, such as chemical composition, physical state, temperature and even gross and ultramicroscopic orientation of the cells and tissues. The data presented for discussion in this paper are concerned with these factors. Because knowledge of the chemical processes that occur normally within the eye is derived frequently from investigations involving experimentally induced changes in ocular tissues, papers on this subject are also discussed.

TEARS

A partial analysis of human tears collected frequently after stimulation with benzyl bromide has shown that the total solids represent 1.87 per cent. Fifty-one per cent of the dissolved material in the tears was found to be dialyzable,[1] and half of this was shown to be sodium chloride. The nondialyzable portion was separated into four fractions by electrophoresis. Three of the components were found to be positively charged, and one was negatively charged. All of the lysozyme activity, which incidentally was shown to differ immunologically from that found in egg white, accompanied the three components that migrated toward the negative pole.

The hydrogen ion concentration of human tears has been determined again and found to have an approximate value of p_H 7.4.[2] Higher p_H values which have been found in the past are attributed to loss of carbon dioxide on standing. Although the osmotic pressure of tears was also measured, no data are presented. It is inferred, however, that tear samples resulting from artificial stimulation were used. Therefore, the observation that tears are isotonic with blood plasma, like that made

From the Howe Laboratory of Ophthalmology, Harvard Medical School.

1. Smolens, J.; Leopold, I. H., and Parker, J.: Studies of Human Tears, Am. J. Ophth. **32**:153 (June, pt. 2) 1949.

2. Hind, H. W., and Goyan, F. M.: The Hydrogen Ion Concentration and Osmotic Properties of Lacrimal Fluid, J. Am. Pharm. A. (Scient. Ed.) **38**:477, 1949.

by Krogh, which has been so widely quoted,[3] has relatively little physiological significance because it does not represent the portion of tears that overlies the cornea.

CORNEA

Previously published studies on the relation of corneal respiration to atmospheric environment, the respiratory rates of various layers of the cornea, the presence and operation of various enzyme systems and the possible sources of nutrition have been reviewed.[3] It is pointed out that there is general agreement among investigators that the epithelium, and perhaps the endothelium, respire at a much greater rate than the stroma and that both surface layers and the stroma are capable of glycolysis. The utilization of oxygen has been found to be dependent on the presence of cytochrome–cytochrome oxidase system. The sources of oxygen and metabolites are the blood, the aqueous humor and the tears.

The results of previous experimental investigations by Cogan and co-workers have been applied to clinical problems, with specific reference to corneal turgescence, epithelial edema, bullous keratopathy and interstitial vascularity of the cornea.[4]

Some concepts of fluid transfer and maintenance of the cornea in a state of deturgescence, evolved by Cogan and Kinsey,[5] have been criticized by Davson.[6] He states that loss of water from the epithelial and endothelial surfaces of the cornea would give rise to an accumulation of salt, which would tend to abolish the difference in osmotic pressure necessary for removal of water. Davson states that the mechanism for removal of salt at the limbus would be inefficient. However, the theory proposed by Cogan and Kinsey does not require that there be a particularly large net transfer of water out of the cornea. A steady state may exist, for instance, in which the osmotic forces arising from difference in concentration between the extracellular fluid of the cornea and the tears, on one side, and the aqueous humor, on the other, will be just slightly greater than the imbibitory power of the corneal tissue, so that there would be no substantial flow of water. A priori, therefore, there seems to be no need of an efficient mechanism for removing salt.

The criticism that the cornea does not swell appreciably after stripping of the epithelium, or in sleep, is a valid one of any theory

3. Duane, T. D.: Metabolism of the Cornea, Arch. Ophth. **41**:736 (June) 1949.

4. Cogan, D. G.: Studies on the Clinical Physiology of the Cornea: The Interrelationship of Corneal Turgescence, Epithelial Edema, Bullous Keratopathy, and Interstitial Vascularization, Am. J. Ophth. **32**:625, 1949.

5. Cogan, D. G., and Kinsey, V. E.: The Cornea: Physiologic Aspects, Arch. Ophth. **28**:661, (Oct.) 1942.

6. Davson, H.: Some Considerations on the Salt Content of Fresh and Old Ox Corneae, Brit. J. Ophth. **33**:175, 1949.

which ascribes an indispensable role to the corneal epithelium in deturgescence of the stroma. It was emphasized earlier, however, that the relative role of the epithelium and endothelium in deturgescing the cornea [5] was not known, and it was demonstrated experimentally that the cornea could be prevented from swelling when only one of the surface membranes was intact, so long as there was also a proper osmotic gradient.[7] Clinically, it appears that the endothelium alone is sufficient for the maintenance of a deturgesced state of the cornea, so that the role played by the epithelium cannot be assessed. If, however, the endothelium becomes impaired, as is the case in the guttate cornea, the importance of the epithelium in preventing corneal swelling becomes apparent. In this condition prevention of evaporation, as with closing of the lids (sleep), characteristically causes edema.

No alternative theory has been proposed to account for the fact that the cornea is normally maintained in a deturgesced state, whereas it swells when immersed in aqueous solutions in vitro. However, it is stated [6] that too little attention has been given to the vital activity of the cellular constituents of the cornea. The experimental determinations reported led to the conclusion that if there is any difference between the concentration of dissolved substances in fluids outside the cornea and that of the extracellular fluid within the cornea the latter is the higher. Thus, the vital activity, if any, would have to overcome not only the imbibitory properties of the corneal tissue but the difference in osmotic pressures as well.

The permeability of the epithelium in the excised cornea was shown to increase as a result of iontophoresis.[8] The increase apparently augments the quantity of material which may be introduced in the eye as a result of iontophoresis.

The water contents of the bovine, rabbit and cat cornea have been found to be 77.8, 77.7 and 76.4 per cent, respectively, and those of the sclera 68.1, 68.3 and 67.0 per cent in the same animals.[9] It was pointed out that the greater water content of the cornea than of the sclera is not inconsistent with its deturgesced state, since corneal tissue greatly increases its state of hydration when pieces are immersed in aqueous solutions, whereas the sclera does not swell significantly when treated similarly. The semipermeable membranes on either side of the cornea are thought to be responsible for the constancy of corneal hydration.

The acetylcholine content of the corneal epithelium has been found to be higher than that of any other tissue, amounting to 100 to 200

7. Kinsey, V. E., and Cogan, D. G.: The Cornea: Hydration Properties of the Whole Cornea, Arch. Ophth. **28**:449 (Sept.) 1942.

8. Dyson, C.: Influence of Iontophoresis on the Permeability of the Excised Cornea, Arch. Ophth. **42**:416 (Oct.) 1949.

9. Duane, T. D.: The Steady State of Corneal Hydration, Am. J. Ophth. **32**:203 (June, pt. 2) 1949.

micrograms per gram in the rabbit.[10] The thiamine content of the epithelium was found to be 26 to 42 micrograms per gram, while the stroma contained approximately 2 micrograms per gram. The concentration of cholinesterase in the epithelium was said to be about three times that in the stroma. The topical anesthetics, cocaine and tetracaine, caused a decrease in the acetylcholine content of the cornea but did not affect the thiamine content.

Further studies have been performed on the localization and identification of phosphatase in the rat cornea.[11] Activity for alkaline phosphatase was demonstrated by histochemical technic in both the nucleus and the cytoplasm when ribose nucleic acid was used as a substrate. The enzyme was activated by the presence of small amounts of glucose and potassium chloride, suggesting that the attack of the tissue on nucleic acid might involve a transphosphorylation, rather than a simple dephosphorylation. The histochemical method was thought to provide information on the integrated action of highly complex systems of enzymes, which may be decomposed into apparently unrelated elements in disorganized tissue brei. The phosphatases in the cornea were not inhibited by agents known to inhibit mitosis, from which observation it was apparent that inhibition of mitosis does not result from disorganization of the nucleic acid phosphatase system.

The relation between nutrition and corneal vascularity has been investigated further.[12] Heavy vascularization, thickening and opacity of the cornea were observed in about 50 per cent of rats aged 41 to 61 days which were raised on a pantothenate-deficient diet. Similar signs were observed in approximately the same percentage of rats aged 45 to 57 days which were raised on a pyridoxine-deficient diet. These investigations extend to four vitamins whose absence in some species produces vascularity; the other two are vitamin A and riboflavin.

A deficiency of tryptophan has been shown to decrease the oxygen consumption and the anaerobic glycolysis of the rat cornea.[13] Other chemical investigations include a study of the deaminating reactions which occur in both the cornea and the choroid.[14]

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10. von Brücke, H.; Hellauer, H. F., and Umrath, K.: Azetylcholin und Aneuringehalt der Hornhaut und seine Beziehungen zur Nervenversorgung, Ophthalmologica **117**:19, 1949.

11. Friedenwald, J. S., and Crowell, J. E.: Histochemical Studies on Nucleic Acid Phosphatase, Bull. Johns Hopkins Hosp. **84**:568, 1949.

12. Bowles, L. L.; Hall, W. K.; Sydenstricker, V. P., and Hock, C. W.: Corneal Changes in the Rat with Deficiencies of Pantothenic Acid and of Pyridoxine, J. Nutrition **37**:9, 1949.

13. de Berardinis, E.: Ricerche sul ricambio della cornea e del cristallino di ratti in carenza di triptofano, Gior. ital. oftal. **2**:350, 1949; abstracted in Ophth. Lit. **3**:555, 1950.

14. Auricchio, G., and Vincentiis, M.: Sulla capacita deaminante dei tessuti oculari, Boll. Soc. ital. biol. sper. **25**:31, 1949; abstracted in Ophth. Lit. **3**:549, 1950.

AQUEOUS HUMOR

Recent experiments have brought the opinions of Duke-Elder and co-workers [15] into closer agreement with those of other investigators [16] who believe that the aqueous humor cannot be regarded as a simple dialysate, but that it is a dynamic fluid having a through and through circulation in the eye and originates in part as a result of secretory processes in the ciliary body. Earlier studies on the chemical composition and osmotic pressure of the aqueous humor, the penetrability of the blood-aqueous barrier by different substances under normal and abnormal conditions and the relation of the dynamics of intraocular fluids to practical problems bearing on variations in intraocular pressure are reviewed.[15]

In a noteworthy paper, Friedenwald [16f] has correlated the studies of various workers on the formation of intraocular fluids and has elaborated his theory of the mechanism of secretion of aqueous humor. He visualizes the formation of unbalanced bicarbonate ions in the epithelium of the ciliary body, a process which takes place as a result of oxidation of cytochrome oxidase by molecular oxygen. The oxygen, he assumes, reacts with water to form hydroxyl ions, which, in turn, combine with carbon dioxide to form bicarbonate ions. In the stroma hydrogen ions are produced as a result of oxidation of a metabolite. These react in the stroma with bicarbonate to form carbon dioxide, thereby producing a net deficit of bicarbonate. The excess bicarbonate ions in the epithelium, he believes, could result in the transfer of cations from the plasma into the posterior chamber. While Friedenwald does not regard this analysis as complete, it represents a definite advance toward an understanding of the chemical reactions that may be involved in the secretory mechanism.

Although the concentration of radioactive tracers can be determined with great accuracy in the fluids of the eye, the topographic relations of atoms within individual structures of the eye can best be shown by

15. Duke-Elder, S.: The Physiology of the Intraocular Fluids and Its Clinical Significance, Tr. Am. Acad. Ophth. **54**:18, 1949. Davson, H.: The Aqueous Humour and the Blood-Aqueous Barrier, Ophth. Lit. **3**:254, 1949.

16. (*a*) Friedenwald, J. S., and Stiebler, R. D.: Circulation of the Aqueous: A Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938. (*b*) Kinsey, V. E., and Grant, W. M.: The Mechanism of Aqueous Humor Formation Inferred from Chemical Studies on Blood-Aqueous Humor Dynamics, J. Gen. Physiol. **26**:131, 1942; (*c*) The Secretion-Diffusion Theory of Intra-Ocular Fluid Dynamics, Brit. J. Ophth. **28**:355, 1944. (*d*) Friedenwald, J. S.: Dynamic Factors in the Formation and Reabsorption of Aqueous Humour, ibid. **28**:503, 1944. (*e*) Bárány, E. H.: The Relative Importance of Ultrafiltration and Secretion in the Formation of Aqueous Humour as Revealed by the Influence of Arterial Blood Pressure on the Osmotic Pressure of the Aqueous, Acta physiol. scandinav. **13**:81, 1947. (*f*) Friedenwald, J. S.: The Formation of the Intraocular Fluid, Am. J. Ophth. **32**:9 (June, pt. 2) 1949.

means of radioautographs. This technic has been successfully employed by von Sallmann and co-workers [17] to trace the movement of sodium in the eye. This substance enters the eye chiefly in the region of the ciliary body and optic nerve. Evidence suggesting that active transport of sodium from the blood to the intraocular fluid occurs across the barrier membranes of the ciliary process was obtained by introducing cyanide as a specific inhibitor of energy-providing reactions. Support for the theory of through and through circulation in the eye was obtained by tracing the movement of sodium from the region of the ciliary body into the anterior chamber. After intravitreal injection, rapid diffusion occurred in the vitreous humor and into the anterior chamber. The movement in the living eye exceeded that in the enucleated globe. Some indication was obtained by the radioautographic technic that the entrance of sodium into the eye was different in the cat than in the rabbit. This observation may account in part for differences in results of studies of aqueous humor dynamics obtained by workers in this country, who used chiefly rabbits, and those in England, where cat eyes have been used most extensively.

Similar conclusions regarding the entrance of phosphate were reached by Palm,[18] who also was successful in making radioautographs. He injected phosphate labeled with radioactive phosphorus intraperitoneally into guinea pigs and observed that the ciliary body was the site of the most intense darkening. He thus confirmed the general view that the main exchange between the blood and the avascular media of the eye takes place through the vascular region in the anterior parts of the uvea. The penetration into the lens was shown to occur chiefly through its anterior surface.

The rate of flow of aqueous humor has been determined in the rabbit,[19] and in the human being.[20] In the rabbit this value was deduced from the rate at which paraaminohippuric acid, radioactive rayopake® (2-methyl-4,6-diketo-5-iodotetrahydropyridone-N-acetic acid) and iodopyracet (diodrast®) leave the anterior chamber of the eye; 1.1 per cent (2.75 microliters) of the aqueous humor was found to leave

17. von Sallmann, L.; Evans, T. C., and Dillon, B.: Studies of the Eye with Radiosodium Autographs, Arch. Ophth. **41**:611 (May) 1949.

18. Palm, E.: The Exchange of Phosphate Between the Blood and the Eye Studied with the Aid of Radio-Autographs, Acta ophth. **27**:267, 1949.

19. (*a*) Bárány, E., and Kinsey, V. E.: The Rate of Flow of Aqueous Humor: Rate of Disappearance of Para-Aminohippuric Acid, Radioactive Rayopake, and Radioactive Diodrast from the Aqueous Humor of Rabbits, Am. J. Ophth. **32**:177 (June, pt. 2) 1949. (*b*) Kinsey, V. E., and Bárány, E.: The Rate of Flow of Aqueous Humor: Derivation of Rate of Flow and Its Physiologic Significance, ibid. **32**:189 (June, pt. 2) 1949.

20. Goldmann, H.: Der Übertritt von Fluorescein aus dem Blut ins Kammerwasser des normalen Menschen, Experientia **5**:295, 1949.

the anterior chamber per minute by flow. In the human being the rate of flow was calculated from the rate of entrance of fluorescein and also found to be 1.1 per cent per minute; this rate in the human eye corresponds to 2 microliters per minute.

The rate of disappearance of sodium from the anterior chamber in the rabbit was again measured and found to be the same as the rate of flow.[19b] From this observation it was concluded that sodium and other electrolytes normally enter the anterior chamber exclusively by flow from the posterior chamber; i. e., none either enter or leave through the iris. Because the rate of disappearance of nonelectrolytes and water from the anterior chamber was shown to exceed the rate of flow—some loss occurring by exchange across the iris—it was concluded that these substances enter both by flow from the posterior chamber and by diffusion from the blood through the iris.

The experimental results reported in these papers quantitatively support the diffusion-secretion theory of the formation of aqueous humor proposed earlier by Kinsey and Grant.[19b, c]

The dynamics of aqueous humor in the rabbit and the human being have been shown to be similar not only by the corresponding values for the rate of flow, but by the observation that the rate of exchange of water [21] is the same as that found previously for the rabbit [22]; i. e., half the water of the aqueous humor is replaced in approximately three minutes.

The permeability characteristics of the blood-aqueous barrier of the young rabbit have been shown to differ significantly from those of the adult rabbit [23] by determining the relative concentration of inulin in the aqueous humor and plasma of rabbits as a function of age of the animal. It was observed that the barrier became progressively less permeable up to the age of 14 days, at which time no appreciable amount of inulin could be recovered in the aqueous humor. The change in permeability was thought to be related to regression of the hyaloid system. These observations indicate the widely different nature of the resulting fluid in a system in which there is a simple barrier of capillary endothelium separating the blood and intraocular fluids, as in the young animal, and one in which there is a highly complex barrier, as in the adult animal.

Extensive further investigations of the kinetics of penetration of various classes of substances into the aqueous and vitreous humors of the cat and rabbit eye have indicated that the barrier separating the

21. Cagianut, B.; Heusser, H. and Eichenberger, K.: Beitrag zum Wasseraustausch zwischen Kammerwasser, Linse und Glaskörper beim Menschen, Experientia **5**:243, 1949.

22. Kinsey, V. E.; Grant, M., and Cogan, D. G.: Water Movement and the Eye, Arch. Ophth. **27**:242 (Feb.) 1942.

23. Kinsey, V. E., and Williamson, M. B.: Investigation of the Blood-Aqueous Barrier in the Newborn: II. To Inulin, Am. J. Ophth. **32**:509, 1949.

aqueous humor from the blood plasma possesses a selectivity capable of discrimination on the basis not only of molecular size, but also of chemical structure.[24] The results also indicated a wide variability between the barrier separating blood, on one hand, and the aqueous humor and the vitreous body, on the other. While an attempt has been made to compare quantitatively the rates of penetration of different substances by calculating the magnitude of a given permeability constant, the results must be considered only as approximate, since evidence of the constancy of the concentration for the various substances in the plasma is lacking and since some of the calculations do,[24a, c] and some do not,[24b, d] include the necessary mathematical adjustment to take into account the effect of flow of aqueous humor on the steady state concentration ratios. For example, the failure to take into account the effect of flow for substances such as sucrose, in which the aqueous humor apparently is rather deficient, can give rise to large errors in calculating permeability constants.

The ratio of the concentration of glucose in the aqueous humor to that in plasma under steady state conditions was found to be about 0.8.[25] Similar values were found for galactose, xylose and arabinose. The rates of penetration of all these sugars were also found to be equal. These results led to the conclusion that the deficit of glucose is not due solely to utilization by the lens or retina, and that this substance must enter the aqueous humor by a diffusional process. Unlike many studies of the sugars in various parts of the eye, the method used for the chemical determination of glucose appeared to be specific, i. e., did not include other reducing substances.

In another paper [26] it was concluded that the low concentration of glucose in the aqueous humor is due mainly, if not entirely, to utilization by the lens. This conclusion was based on comparative measurements of the concentration of total reducing substances in the aqueous humor of aphakic and normal eyes, it being reasoned that if the deficiency of

24. (*a*) Davson, H.; Duke-Elder, W. S.; Maurice, D. M.; Ross, E. J., and Woodin, A. M.: The Penetration of Some Electrolytes and Non-Electrolytes into the Aqueous Humour and Vitreous Body of the Cat, J. Physiol. **108**:203, 1949. (*b*) Ross, E. J.: The Formation of the Intra-Ocular Fluids: Studies of the Urea Component of the Aqueous Humour, Brit. J. Ophth. **33**:310, 1949. (*c*) Duke-Elder, S.; Davson, H., and Maurice, D. M.: Studies on the Intra-Ocular Fluids: Penetration of Certain Ions into the Aqueous Humour and Vitreous Body, ibid. **33**:329, 1949. (*d*) Duke-Elder, S.; Davson, H., and Woodin, A. M.: Studies on the Intra-Ocular Fluids: Penetration of Some Nitrogenous Substances into the Intra-Ocular Fluids, ibid. **33**:452, 1949.

25. Harris, J. E., and Gehrsitz, L. B.: The Movement of Monosaccharides into and out of the Aqueous Tumor, Am. J. Ophth. **32**:167 (June, pt. 2) 1949.

26. Duke-Elder, S., and Davson, H.: Studies on the Intra-Ocular Fluids: Reducing Substances in the Aqueous Humour and Vitreous Body, Brit. J. Ophth. **33**:21, 1949.

glucose were due primarily to utilization by the lens, its concentration should be more like that of the blood after lens extraction. The concentration was shown to be elevated only in the cat eye. In the rabbit eye the average concentration of "glucose" was less (117 mg., as compared with 124 mg., per 100 cc.) after lens extraction. While it may be true, as the authors stated, that "the *increase* in concentration of glucose in aphakia in this animal is masked by the decrease in ascorbic acid" (not determined), and that some glucose is lost to the vitreous humor in aphakic eyes, the evidence for the conclusion seems tenuous.

In any event, it is clear that utilization of glucose by lens metabolism will contribute toward any deficit of this substance existing in the aqueous humor. The question is how much of the deficit can be explained on this basis and how much is due to retention.[14b] It would seem that, considering the quantities of other reducing substances present in aqueous humor, conclusions cannot be drawn concerning the exact quantitative effect of the metabolism of glucose on the steady state ratios unless methods specific for this substance are used. Further evidence for utilization of glucose by the retina and for the entry of sugars into the aqueous humor by diffusional processes has been presented.[26]

Loss of sodium and chloride from the aqueous humor to the plasma as a result of dialysis indicated that the aqueous humor is not in thermodynamic equilibrium with the blood.[27] The concentration of chloride in the aqueous humor of dogs was again found to exceed that of plasma by about 7 per cent (9 millimoles per liter), whereas the excess of sodium was found to be only approximately 3 millimoles per liter. These observations led to the conclusion that there must be some organic cation present in the aqueous humor. Other investigators,[28] however, have found that the concentration of chloride in the plasma of the dog is equal to that in aqueous humor and have questioned the adequacy of the method used to determine chloride in dog plasma. In any event, in view of the possibility that some other anion, for example, bicarbonate, might be sufficiently deficient in the aqueous humor to meet electrostatic requirements, one is not forced to make the unlikely postulate of the presence of an unknown organic cation in a concentration of the order of magnitude of 9 millimoles per liter. Actually, the reverse is true in the rabbit; i. e., the concentration of chloride is lower in the aqueous humor than in plasma,[28] but the deficiency is made up chiefly by an excess of bicarbonate ions.[29]

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27. Duke-Elder, S., and Davson, H.: Studies on the Intra-Ocular Fluids: Dialysation of Aqueous Humour Against Plasma, Brit. J. Ophth. **33**:593, 1949.

29. Kinsey and Bárány.[10b] Kinsey, V. E.: The Chemical Composition of the Aqueous Humor and Plasma of the Rabbit, to be published.

28. Kinsey, V. E.: Aqueous Humor/Plasma Chloride Ratios in Rabbits, Dogs and Human Beings, J. Gen. Physiol. **32**:329, 1949.

The penetration of sulfonamide drugs into the aqueous humor has been studied from two points of view. In the first study,[30] the object was to extend investigations of the barrier between blood and intraocular fluids to include substances having high lipid solubility. In the second study,[31] the penetration of the blood-aqueous barrier by some of the newer sulfonamide drugs was discussed with respect to potential therapeutic usefulness.

A comparison of the rates of penetration of the sulfonamide drugs with those of substances that had previously been determined suggested that the rate of penetration into the aqueous humor depends on lipid solubility,[30] although it is pointed out that the relative rates of penetration of the individual substances are not completely predictable from their ether-water partition coefficient or from the percentage dissociation. Evaluation of the significance of the relative rates of penetration of the different sulfonamide drugs tested would have been possible had the authors included any experimental data on concentration used for calculating these rate constants.

In the rat both sulfanilamide and sulfamerazine were found to attain higher concentrations than sulfadiazine and sulfamethazine (N^1-[4,6-dimethyl-2-pyrimidyl]sulfanilamide), but in the rabbit the concentrations of both sulfadiazine and sulfamethazine exceeded that of sulfamerazine.[31] It was concluded that sulfamerazine is superior to sulfamethazine, judging by the levels and persistence obtained in the rat—a superiority not apparent in the rabbit. Sulfathiazole was found to be the least satisfactory drug in both the rat and the rabbit from the clinical viewpoint.

The permeability of the blood-aqueous barrier has been shown to be increased in scurvy and transiently increased after intravenous administration of vitamin K preparations,[32] owing perhaps to the histamine-like effect of vitamine K on capillaries. Vitamin P_2 on the other hand, in doses of 200 mg. daily, was shown to decrease the permeability slightly in normal subjects and markedly in subjects with diabetic retinitis.[33] The permeability has also been shown to increase after the intravenous injection of acacia, as demonstrated by the increased protein content of

30. Davson, H.: The Penetration of Some Sulphonamides into the Intra-Ocular Fluids of the Cat and Rabbit, J. Physiol. **110**:416, 1949.

31. Sorsby, A.: Concentration in the Aqueous of Various Sulphonamides After Systemic Administration, Brit. J. Ophth. **33**:347, 1949.

32. Simonelli, M.: Ricerche sulla permeabilità della barriera emato-oftalmica: Influenza della somministrazione di vitamina K, Gior. ital. oftal. **2**:329, 1949; abstracted in Ophth. Lit. **3**:550, 1950.

33. Simonelli, M.: Ricerche sulla permeabilità della barriera emato-oftalmica: Influenza della somministrazione della vitamina P_2, Gior. ital. oftal. **2**:185, 1949; abstracted in Ophth. Lit. **3**:103, 1949.

the aqueous humor.[34] From the observation that acacia disappeared gradually from the aqueous humor, it was concluded that the substance must escape through drainage channels. The same paper included a thorough review of the literature on the formation of the aqueous humor.

VITREOUS HUMOR

Investigations of the physical-chemical properties of the vitreous humor have led Pirie[35] to conclude that the presence of the insoluble structure of the protein of the vitreous humor helps to maintain aggregated hyaluronic acid and the latter helps to maintain the structural protein. Thus, liquefaction of the insoluble protein is slowed down by the presence of aggregated hyaluronic acid, and disaggregation of hyaluronic acid is retarded by the presence of insoluble protein. The vitreous humor is conceived as being made up of a network of fibrils which are the prolongation of cells, and the network is permeated by a viscous fluid or jelly, consisting of aggregated hyaluronic acid, soluble proteins and substances of small molecular weight. Hydrolysis of the fibrillar protein by enzyme preparations containing collagenase causes liquefaction of the humor. Hyaluronidase, however, had no liquifying effect when injected into the vitreous humor of ox eyes, presumably because the structure of the humor prevents rapid diffusion of the enzyme. In the living rabbit, however,[36] injections of hyaluronidase into the vitreous humor were shown to disaggregate the hyaluronic acid; the acid remained in this state for at least a month. The reappearance of the aggregated hyaluronic acid indicated that this substance can be produced in or secreted into the vitreous humor during life. It is of possible clinical interest that the injection of rabbit testis hyaluronidase into the vitreous humor of the rabbit was found to cause a prolonged inflammatory reaction, as shown by elevation of the nitrogen content of both the aqueous and the vitreous humor.

The diffusion rate for the penetration of homologous hemoglobin in undamaged preparations of pig and steer vitreous humors was observed to increase with temperature and after autolysis.[37] The simultaneous injection of hyaluronidase had no effect on the rate of diffusion of hemoglobin or trypan (Niagara) blue, nor did alteration of p_H from 6 to 8 change the diffusion rate. The surface condensation layer of vitreous

34. Michiels, J.: Étude expérimentale sur la formation de l'humeur aqueuse, Ophthalmologica, supp. 34, 1949.

35. Pirie, A.: Ox Vitreous Humour: Hyaluronic Acid Relationships, Brit. J. Ophth. **33**:271, 1949.

36. Pirie, A.: Effect of Hyaluronidase Injection on the Vitreous Humour of the Rabbit, Brit. J. Ophth. **33**:678, 1949.

37. von Sallmann, L.: Experimental Studies on Vitreous: Experiments on Diffusion in the Vitreous and on Permeability of Its Surface Condensation Layer, Arch. Ophth. **42**:583 (Nov.) 1949.

humor was shown to be less permeable for hemoglobin than was the vitreous humor itself. Hydrochloric acid was found to penetrate the surface layer and to diffuse at a higher rate than did sodium hydroxide. Similarly, acetic acid moved faster than did ammonium hydroxide.

The composition of the vitreous humor corresponds in many respects to that of the aqueous humor. A striking point of dissimilarity between these fluids is the difference in the phosphate content.[38] The relative concentrations of orthophosphate in the aqueous and vitreous humors and the plasma of the rabbit have been found to be 32.6, 9.9 and 58.4 micrograms of phosphorus, respectively, per milliliter.

Measurements of the distribution of phosphate in the vitreous humor in the ox eye have shown that the concentration rises significantly in this fluid in the vicinity of the ciliary body.[38] These observations show clearly that the liquids permeating the structure of the gel body are not identical with those of the aqueous humor. Utilization of phosphate by various tissues surrounding the vitreous humor was cited as the most probable explanation of the deficiency of this substance in this body fluid.

LENS

The chloride content of the lens in an excised eye was found to increase on standing.[39] Diffusion of radioactive sodium and bromine into the lens occurred more rapidly in vitro than in vivo, indicating the rapidity with which postmortem changes occur in the lens. The "readily available space" of the lens was estimated to be between 5 and 6 per cent of the volume of the adult sheep or rabbit lens.

The water contents of bovine, rabbit and cat lenses of various ages were found to vary inversely with the age and weight of the lenses, the absolute values varying from 70 to 60 per cent.[40] The oxygen uptake of various portions of the rabbit lens was reinvestigated.[41] The young rabbit lens at 37 C. in air was shown to have an oxygen consumption rate of 0.09 microliters per milligram of dry weight per hour. On rupture of the capsule the oxygen uptake was increased two to fourfold. The capsule itself and the nucleus had a negligible respiration, whereas the teased fibers of the rabbit lens had an oxygen consumption rate of 0.145 microliters per milligram of dry weight per hour.

The effect of hyaluronidase on the permeability of the lens capsule was investigated by determining the opacity of the surrounding fluid

38. Palm, E.: The Phosphate Content of the Vitreous Body, Acta ophth. **27**:553, 1949.

39. Langham, M., and Davson, H.: Studies on the Lens, Biochem. J. **44**:467, 1949.

40. Ely, L. O.: Metabolism of the Crystalline Lens: Water Content and Growth Rate, Am. J. Ophth. **32**:215 (June; pt. 2) 1949.

41. Ely, L. O.: Metabolism of the Crystalline Lens: Respiration of the Intact Lens and Its Separated Parts, Am. J. Ophth. **32**:220 (June; pt. 2) 1949.

or by measuring the protein content of this fluid after immersion of lenses in distilled water and isotonic sodium chloride solution.[42] Hyaluronidase [42] and paracentesis were shown to increase the permeability.[43] Incidentally, a similar effect was noted on the membranes of the urinary bladder. The oxygen consumption and the anaerobic glycolysis of the lens were decreased in animals fed diets deficient in tryptophan.[44]

The presence of a phosphoprotein in ox and sheep lenses was revealed by slow alkaline hydrolysis and also by trypsin digestion (ox lenses only).[44] A mean value of about 8 mg. per 100 Gm. of fresh lens tissue was obtained. The nucleic acid of the lens seems to be entirely in the ribonucleic fraction.[45] There are 42 to 47 mg. of this substance per 100 Gm. of fresh tissue in the ox and 33 to 36 mg. in the sheep.

The cataractogenic properties of substances chemically related to naphthalene have been investigated in rats.[46] Cataracts were observed in all rats fed β-tetralol[a] (1,2,3,4-tetrahydro-β-naphthol) in dosage levels of 0.25 per cent or more. They appeared as a perinuclear layer regularly three weeks after institution of the diet, and the lenticular changes were observed to be essentially identical with those in rats fed naphthalene. No permanent irreversible damage to the lenticular epithelium was observed even after prolonged β-tetralol[a] poisoning, nor was any effect observed on either the rate of development or the severity of the cataracts following treatment of the cataracts with dimercaprol injection. Diets containing 50 per cent protein, methionine, cystine, riboflavin and ascorbic acid in high levels were also ineffective in influencing the production of cataracts. Some 25 other derivatives of naphthalene were tested, and several, 1,2,3,4-tetrahydro-2-naphthylpropionate and β-naphthylsalicylate, as well as β-tetralol,[a] had approximately four times the cataractogenic potency of naphthalene itself.

PHOTOCHEMISTRY OF VISION

(This section was written by Dr. Ruth Hubbard.[47])

During the past year some progress has been made with the fundamental chemistry of the reactions underlying rod vision.

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42. Seifter, J.; Baeder, D. H., and Dervinis, A.: Alteration in Permeability of Some Membranes by Hyaluronidase and Inhibition of This Effect by Steroids, Proc. Soc. Exper. Biol. & Med. **72**:136, 1949.

43. Auricchio, G.: La permeabilità al glucosio della capsula lenticolare dopo cheratocentesi, Boll. d'ocul. **28**:161, 1949; abstracted in Ophth. Lit. **3**:444, 1949.

44. Mandel, P.; Nordmann, J.; Zimmer, J., and Harth, S.: A Phosphoprotein in the Lens of the Eye, Nature, London, **164**:794, 1949.

45. Mandel, P.; Nordmann, J., and Zimmer, J.: Acide nucléique du cristallin, Compt. rend. Acad. d. sc. **228**:516, 1949.

46. Fitzhugh, O. G., and Buschke, W. H.: Production of Cataract in Rats by β-Tetralol and Other Derivatives of Naphthalene, Arch. Ophth. **41**:572 (May) 1949.

47. Biological Laboratories, Harvard University, Cambridge, Mass.

Morton and colleagues, in Liverpool, had shown that one of the products of bleaching rhodopsin, retinene$_1$, is the aldehyde of vitamin A_1.[48] This substance can be readily obtained from vitamin A_1 by mild oxidation procedures.[49] The synthetic product was shown to possess properties identical with the natural material except for one property of particular interest. The natural mixture of retinene$_1$ and protein which results from bleaching rhodopsin behaves as a p_H indicator and hence has sometimes been called "indicator yellow." The crude retinene$_1$ which was extracted from the retina with fat solvents also possesses this property but loses it on chromatographic adsorption. Synthetic retinene$_1$ displayed no indicator properties.[49b]

Morton and co-workers have now shown that the p_H indicator property accompanies certain forms of combined retinene$_1$. Retinene$_1$ condenses spontaneously at room temperature with a number of amino compounds and when so coupled acts as a p_H indicator. It reacts in this way with a number of amino acids and proteins and with certain aromatic amines. When coupled with these substances, retinene$_1$ yields absorption maxima in alkaline solution at 360 to 385 millimicrons and in acid solution at 400 to 535 millimicrons. It is postulated that in these complexes two molecules of retinene$_1$ attach to the same amino nitrogen atom. Structural possibilities for some of these interactions are discussed.[50]

Sharp, narrow absorption bands were found to appear in various portions of the spectrum when vitamin A_1 or retinene$_1$ was dissolved in concentrated sulfuric or syrupy phosphoric acid. It is suggested that these bands may bear some relation to the "modulators" which Granit had postulated to explain hue differentiation in color vision. As the authors pointed out, however, the conditions for producing these substances are grossly unphysiologic.[51]

With the identification of retinene$_1$ as vitamin A_1 aldehyde, it became clear that the conversion of retinene$_1$ to vitamin A_1 which occurs in the retina is a reduction. Wald and Hubbard have shown that this process is catalyzed by an enzyme system in which reduced cozymase (DPN-H_2)

48. Morton, R. A., and Goodwin, T. W.: Preparation of Retinene in Vitro, Nature London **153**:405, 1944.

49. (*a*) Ball, S.; Goodwin, T. W., and Morton, R. A.: Studies on Vitamin A: The Preparation of Retinene$_1$—Vitamin A Aldehyde, Biochem. J. **42**:516, 1948. (*b*) Wald, G.: The Synthesis from Vitamin A_1 of "Retinene$_1$" and of a New 545 mμ Chromogen Yeilding Light-Sensitive Products, J. Gen. Physiol. **31**:489, 1948.

50. Ball, S.; Collins, F. D.; Dalvi, P. D., and Morton, R. A.: Studies in Vitamin A: Reactions of Retinene$_1$ with Amino Compounds, Biochem. J. **45**:304, 1949.

51. Ball, S., and Morton, R. A.: Studies in Vitamin A: Vitamin A_1 and Retinene$_1$ in Relation to Photopic Vision, Biochem. J. **45**:298, 1949.

serves as coenzyme.[52] The reaction involves the transfer of two hydrogen atoms from reduced cozymase to retinene$_1$, reducing it to vitamin A$_1$:

$$C_{20}H_{28}CHO \text{ (retinene}_1\text{)} + \text{DPN-H}_2 \rightarrow C_{20}H_{28}CH_2OH \text{ (vitamin A}_1\text{)} + \text{DPN}$$

The components of this enzyme system have since been brought into free solution: the apoenzyme, retinene reductase; the coenzyme, DPN-H$_2$, and synthetic retinene$_1$. When these three solutions are mixed, the retinene$_1$ is reduced quantitatively to vitamin A$_1$. A similar system, which reduces retinene$_2$ to vitamin A$_2$, can be made up from components of the porphyropsin cycle found in the retinas of fresh water fishes. In this case the apoenzyme is obtained from fresh water fish retinas; the coenzyme is again DPN-H$_2$, and the substrate, synthetic retinene$_2$. The apoenzymes from the rhodopsin and porphyropsin cycles are interchangeable; i. e., one need postulate only a single apoenzyme, called retinene reductase. This enzyme system introduces a new vitamin into the chemistry of rod vision, for the central component of cozymase is nicotinamide, the antipellagra factor of the vitamin B complex. In this system, therefore, a member of the vitamin B complex acts to regenerate the A vitamins.[53]

Some years ago Hecht showed that the bleaching of rhodopsin in white light can proceed as though this were a simple photochemical reaction, proportional in rate to the intensity of the light and independent of the temperature. It has also been known since the work of Kühne that rhodopsin can be bleached in the dark by warming to temperatures over 50 C. Recently the apparent activation energy for the bleaching of rhodopsin by heat was determined and found to be about 45,000 calories per mole.[54] It has now been shown that if rhodopsin is irradiated with red light, in which case the quanta have an energy content less than 45,000 calories per mole, a temperature coefficient appears in bleaching, which increases with the wavelength of the light (i. e., as the quanta grow smaller). The appearance of a temperature coefficient in red light is evidence that part of the energy of activation for the bleaching of rhodopsin is supplied by the internal energy of the molecule. From these measurements it was concluded that about 45,000 calories per mole are required to bleach rhodopsin, whether this is supplied by light or by internal energy or by a combination of the two. Rod vision is known to extend into the infra-red region to at least 1,050 millimicrons; and if these relations persist, it seems probable that at this wavelength almost

52. Wald, G., and Hubbard, R.: The Reduction of Retinene$_1$ to Vitamin A$_1$ in Vitro, J. Gen. Physiol. **32**:367, 1949.

53. Wald, G.: The Enzymatic Reduction of the Retinenes to the Vitamins A, Science **109**:482, 1949.

54. Lythgoe, R. J., and Quilliam, J. P.: The Thermal Decomposition of Visual Purple, J. Physiol. **93**:24, 1938.

half the energy of activation for the bleaching of rhodopsin comes from the internal energy of the molecule.[55]

A visual pigment has been described in the retina of the squid which resembles rhodopsin in its absorption spectrum, but which has been reported not to be affected by light.[56] It has now been shown that the squid retina possesses a pigment which has all the essential properties of vertebrate rhodopsin. It bleaches in the light to yield retinene$_1$ and protein. The spectrum of this pigment is of the same shape as that of vertebrate rhodopsin but is slightly displaced toward shorter wavelengths. The temperature characteristics of the formation of retinene$_1$ are somewhat different from those of vertebrate rhodopsin.[57]

An attempt has been made to deduce the molecular weight of rhodopsin from the shape and position of its absorption band at 500 millimicrons.[58] The theoretical basis of this derivation has, however, been seriously criticized.[59] It is difficult in any case to imagine how the molecular weight of a conjugated protein could possibly be derived from the spectrum of its prosthetic group.

The suggestion has been made that the yellow pigment of the human macula, previously shown to be xanthophyll, aids the respiration of the central retina by being reversibly oxidized and reduced.[60] No evidence exists, however, that xanthophyll participates in oxidation-reduction reactions in any tissue, whether plant or animal; nor is it clear how even the most efficient of redox pigments could possibly aid respiration if, as is assumed in this paper, the central retina suffers from a lack of oxygen.

Papers presented at the Cambridge Conference on Colour Vision held in 1947 have now appeared as volume 3 of *Documenta ophthalmologica*.[61] They include a review of the literature on photochemistry of vision to 1947.

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55. St. George, R. C. C.: Interplay of Light and Heat in Bleaching Rhodopsin, Federation Proc. **8**:137, 1949.

56. Bliss, A. F.: The Absorption Spectra of Visual Purple of the Squid and Its Bleaching Products, J. Biol. Chem. **176**:563, 1948.

57. St. George, R. C. C., and Wald, G.: The Photosensitive Pigment of the Squid Retina, Biol. Bull. **97**:248, 1949.

58. Weale, R.: Absorption Spectra, Molecular Weights and Visual Purple, Nature, London **163**:916, 1949.

59. Collins, F. D., and Morton, R. A.: Absorption Spectra, Molecular Weights and Visual Purple, Nature, London **164**:528, 1949.

60. Dartnall, H. J. A., and Thomson, L. C.: Retinal Oxygen Supply and Macular Pigmentation, Nature, London **164**:876, 1949.

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Correspondence

OCCLUDED NASOLACRIMAL DUCTS IN INFANTS

To the Editor.—In a recent article by Dr. Martin P. Koke, entitled "Treatment of Occluded Nasolacrimal Ducts in Infants," published in the April 1950 issue of the ARCHIVES, page 750, the author reports his experience in the treatment of congenital impatency of the nasolacrimal duct and discusses an article on the same subject published by us (Congenital Impatency of Nasolacrimal Duct, ARCH. OPHTH. **39:** 193 [Feb.] 1948). In his article Koke states, "In none of the cases reported by Guerry and Kendig did treatment with massage and local antiseptics, as prescribed by them, for an average time of 2.3 months, correct the occlusion." This is the exact antithesis of our statement, for in every case in our series, 12 in number, the condition cleared under conservative treatment. Koke also takes issue with our thesis that probing through the upper punctum results in the creation of fewer false passages. His reason for this statement is that "the danger of making a false passage exists before the probe reaches the medial wall of the sac," thus implying that a false passage rarely occurs except in the canalicular region. A quick reference to the anatomy of this region will reveal at once the fallacy of this statement. Practical evidence also indicates that most false passages occur along the wall of the sac or the nasolacrimal duct, since it is rare indeed for irrigating fluid to pass into the tissues alongside a perforated canaliculus, while in many cases in which patency is not established (those in which the inferior meatus is not explored at the time of the probing) false passages must of necessity have been made; and these can only have occurred along the nasolacrimal duct or sac, since no fluid is seen in the canalicular region.

In regard to the statistics which Koke has analyzed in his article, a proper evaluation would reveal that, while he advocates early probing, his statistics show that conservative treatment would be equally efficacious. He reports 116 cases of congenital impatency of the nasolacrimal duct. In 14 of these the condition was cured by repeated irrigations, while in 102 treatment was by probing. In all but 14 of these 102 cases cure was effected by a single probing. Of the 14 cases in which a single probing was not effective, the condition in three was never cured in spite of repeated probings. When Koke's cases are analyzed according to the age at which probing was done, it is found that 85 of his patients, or 73 per cent, were under 6 months of age. According to our statistics, in the greater proportion of these infants the occlusion would have cleared with conservative treatment. Of the 31 remaining patients, who were over 6 months of age, 14 required multiple probings before patency was established; and in three of these 14 patency was never established. It seems to us, therefore, that Koke's figures speak eloquently for probing with the use of general anesthesia, this being particularly true in cases in which the procedure is repetitive. If this procedure is carried out and the inferior meatus investigated, patency can be established after a single probing in practically 100 per cent of cases. In our experience,

we have had to reprobe in only one case, and in this instance the inferior meatus had not been explored. When the duct was reprobed and the inferior meatus investigated, the probe was found to be covered with redundant nasal mucous membrane, as described graphically by Larsen, and patency was established by removing this membrane with the submucous elevator, as described in our article.

Since the publication of our original article, we have increased our series on incidence of congenital impatency to 1,000 and have found 57 cases of impatency, or 5.7 per cent (*J. Pediat.* **36:** 212-213 [Feb.] 1950). This figure corresponds closely to the incidence of 6 per cent reported in our original series. By more careful instruction of the mothers in Crigler's method of massage, we have also found that in most of our cases the ducts are clear by the second month, and it is rare indeed that one comes to probing.

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News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Grants-in-Aid for Ophthalmologic Research.—The National Council to Combat Blindness, Inc., continuing its established policy of financing ophthalmologic research, announces that requests for grants-in-aid awards for the period July 1951 to June 1952 are now being accepted. Applications should be in the office of the Council not later than March 1, 1951. Appropriate forms may be obtained by writing to the secretary, National Council to Combat Blindness, Inc., 1186 Broadway, New York 1.

International Association for Prevention of Blindness.—The offices of the International Association for Prevention of Blindness have been transferred to the office of the president, Dr. P. Bailliart, 47 Rue de Bellechasse, Paris, France.

Fourth Pan-American Congress of Ophthalmology.—The Fourth Pan-American Congress of Ophthalmology will meet in México, D. F., Mexico, from Jan. 6 to 12, 1952.

International College of Surgeons.—The fifteenth annual assembly of the United States chapter of the International College of Surgeons will be held in Cleveland, October 31 to November 3, with headquarters at the Cleveland Hotel.

Surgical clinics will be held in several Cleveland hospitals on Monday, October 30. All scientific sessions will be held at the Cleveland Public Auditorium from 9:00 a. m. to 5:00 p. m. Tuesday through Friday. An excellent program has been arranged.

Reservations may be secured by writing to the Committee on Hotels, International College of Surgeons, 511 Terminal Tower, Cleveland 13. Preliminary programs may be obtained from the central office, 1516 Lake Shore Drive, Chicago 10.

Annual Clinical Conference, Wills Hospital.—The third annual clinical conference of the Wills Hospital, Philadelphia, will be held at the hospital March 16 to 17, 1951. As in other years, papers which reveal the latest developments in ophthalmologic treatment and procedures will be presented by many of the nation's outstanding ophthalmologists.

SOCIETY NEWS

Société française d'ophthalmologie.—This society usually holds its annual meeting in May, but in 1950 it met at the end of July, immediately after the International Congress of London. Thanks to this arrangement, a considerable number of non-French ophthalmologists were able to attend; in fact, the Paris meeting was as international as the London one.

The yearly symposium, an 800 page volume, on "Night Vision and Its Disturbances," was conducted by Gaëtan Jayle and Albert Ourgaud (both of Marseilles). The physiological and physical aspects of the problem were more carefully dealt with than is usual in ophthalmological publications. The subject of this symposium was discussed at length, and during this discussion Prof. Hans Goldmann, of Berne, presented his new automatic adaptometer. Like many other objective measures advocated by Professor Goldmann, it is based on the appearance of optic nystagmus.

Besides the day devoted to the symposium on night vision, there were four other sessions. Monday was devoted to neuro-ophthalmology. Ten papers were read, of which the most important are listed here. Petit-Dutaillis and L. Guillaumat (Paris) described the progressive changes in the fundus after a caroticojugular anastomosis in a patient with thrombosis of the carotid artery. Louis Paufique and R. Etienne (Lyon) found anomalies of the cervical intervertebral spaces of patients with optic neuritis and claimed that disease of the intervertebral disks should be considered an etiologic factor in some cases. An interesting discussion on aqueous veins followed a paper by Nico Trantas (Athens, Greece), on the pressure in retinal vessels after compression of the cavernous sinus.

On Tuesday there were 11 papers on the retina, most of them very interesting. C. L. Scheppens (Nahant, Mass.) discussed inflammatory conditions of the ora serrata; Georges Bonamour (Lyons), the retinopathy observed in terminal stages of patients with intestinal cancer (retinitis cachecticorum). Calmettes, Darnaud and Deodati (Toulouse) gave their findings in 500 diabetic patients, 200 of whom (40 per cent) had retinopathy. The incidence of age, duration of the diabetes and treatment were considered. A case reported by Arthur Bedell (Albany, N. Y.) illustrated that angioid streaks are not due to trauma; excellent kodachrome slides showed the evolution of lesions in both eyes of his patient. As usual, the subject of retinal detachment gave rise to a lengthy and passionate discussion. H. Arruga (Barcelona) read a paper on an unusual form of bilateral hereditary detachment, and C. Dejean (Montpellier) illustrated with cases in which a flap tear was nonvisible, the flap being at first reapplied and the hole apparently closed. But it was Mme. Sedan-Bauby (Marseilles) who started a lively exchange of opinions when she reported on a patient with a retinal tear whom she had under observation for three years without detachment and in whom a detachment developed after operation for that tear. Opinions were divided. Many advised operating on all tears, even when no detachment was as yet present. Others were for observing the patient and operating only if the retina began to detach. A middle of the way attitude, which seemed to be approved by many, was that there is no single rule, but that each case should be examined on its own merits and that a careful study of the field might show whether the neighboring portion of the retina was quite normal or already affected. A careful search for uveal lesions around the tear and for secondary tears also might help to decide. G. B. Bietti (Pavia) read an interesting paper on his physiological and clinical researches with oxygen; he stressed particularly the temporary improvement in central field defects during inhalation of oxygen.

On Thursday morning nine papers dealing with the uvea were read. René and Michel Onfray (Paris) stressed the atypical cases of tuberculous uveitis (in which no tubercle bacilli are found). P. Matteucci (Turin) started an interesting discussion on Fuchs's heterochromia. The consensus was that this was not an inflammatory condition, but one due to organic involvement of the nervous system. Another lively discussion was started by Gabriel Sourdille (Nantes) when he advised an inferior incision if a cataract had to be removed in a patient previously operated on for glaucoma. Emilio Raverdino (Milan) read a paper on anticoagulating medication in inflammatory diseases of the uvea.

On Thursday afternoon there was a last session, with nine papers on various subjects. One of the most interesting was that by Alfred Brini (Strasbourg), who studied experimentally, by grafting optic vesicles at different stages of their development, the origin of the choroidal melanoblast. In his opinion, it proceeds from the ganglion ridge and is therefore of neural origin. Dinko Sakic, of Split, advised parenteral injections of cod liver oil for vernal conjunctivitis. Erik Godfredsen (Copenhagen) discussed the etiologic factors which might explain the coexistence noted by him of glaucoma and Ménière's disease. A. Busacca and Nóbrega (São Paulo) reported on 23 cases of uveitis in patients giving a positive reaction in the test for toxoplasmosis and discussed the etiology. Albert Bronner (Strasbourg) gave an interesting and well illustrated report on the condition of the fundus in "blue babies" before and after the operation.

Altogether, 40 papers were read. They will appear in the volume of the *Transactions*, which should come out toward the end of 1950. The *Transactions*, together with the yearly symposium, are, of course, sent to all members of the society. Nonmembers can obtain them by applying to the publisher, Masson & Cie, 120 Boulevard Saint-Germain, Paris, France.

The afternoon of Wednesday was entirely devoted to films—some of them already seen in America, others made in Europe: Albert Favory (Paris), operation for ptosis; Wendell L. Hughes (Hempstead, N. Y.), operation for trichiasis; Henry Minsky (New York), Zinn's ligament and the zonular spaces; Louis Paufique (Lyons), lamellar keratoplasty; John M. Converse (New York), skin grafts for ectropion; G. E. Jayle (Marseilles), perilimbic grafts and lamellar keratoplasty; Derrick Vail (Chicago), the Smith-Indian cataract extraction; Conrad Berens (New York), cycloelectrolysis in glaucoma; Ramon Castroviejo (New York), keratoplasty; Mario Amenabar (Santiago, Chile), instrumentation for cataract extraction.

On Monday afternoon there were operative sessions in various hospitals. In the Lariboisière Hospital, Dr. Paul Boeder and Dr. Hermann M. Burian (Boston) gave a lecture on aniseikonia and demonstrated the latest model of space eikonometer made by the American Optical Company.

The social activities, as usual were well attended. On Tuesday afternoon a special train took members of the Congress out to Chartres. The Cathedral was visited under the guidance of Mr. Marcel Aubert,

the president of the French Archeological Society, and its collection of twelfth and thirteenth century stained glass windows, which is unique, was seen by the glorious light of a sunny afternoon. The usual banquet was held on Wednesday night and was presided over by Dr. Conrad Berens, of New York, president of the Pan-American Association. The Société française d'ophtalmologie elected as members of honor Dr. A. Trantas, of Athens; Sir Stewart Duke-Elder, of London, and Dr. Arnold Knapp, of New York.

The next, the fifty-eighth annual, meeting, will be held in Paris in May 1951.

EDWARD HARTMANN, M.D.

Obituaries

HARRY SEARLS GRADLE, M.D.

1883-1950

When Dr. Harry S. Gradle became incapacitated by a cardiovascular ailment, on Nov. 1, 1945, one of the fullest and richest ophthalmologic careers came to an end. How hard he found it to give up his place in the center of the field and to retire to the sidelines, he probably would have never told us. As it happened, his speech became impaired to such an extent that, for a while, he was not able to tell us what was going on in his mind. His intimate friends could see the twinkle return to his eyes not very long after he and Audrey Gradle had settled down in their new home in Sherman Oaks in the San Fernando Valley, from where he watched the progress of ophthalmology with a keen eye and ear for more than three years. His health seemed to improve, and for a time he became a spiritual leader again, this time in a group of similarly handicapped people. Shortly after Christmas 1949 his condition took a turn for the worse, and on May 25, 1950 a kind, painless death relieved him of a steadily increasing physical incapacity.

Dr. Gradle was born in Chicago of half-German, half-Irish, but wholly medical, parentage, on Dec. 31, 1883. His father, Dr. Henry Gradle, was a European-born and largely European-trained ophthalmologist, who had gained prominence in Chicago as a clinician as well as a bacteriologist. Harry Gradle's mother, Fanny Searls, was one of the first woman graduates of the Medical School of Northwestern University. Harry S. Gradle received his college education at the University of Michigan and his undergraduate medical education at Rush Medical College, from which he graduated in 1908. After serving a one year's internship at the North Chicago Hospital, he went abroad and spent most of the period between 1909 and 1914 at various European medical centers, applying himself arduously to the study of ophthalmology. He practiced in Chicago up to the time of the entry of the United States into the first world war, when he applied for and received a commission in the Medical Corps of the United States Army. He stayed in active service, in the United States and in France, until May 1919. In the Medical Reserve, he was promoted to the rank of Colonel and to the position of Division Surgeon for the 86th Infantry Division in 1924. From this position he retired in 1939 but remained keenly interested in military ophthalmology throughout his life. During World War II he acted as Consultant to the Surgeon General, United States Army.

It is significant that during his Army life he conceived his first major organizational idea, which already bore all the characteristics of his later ideas: an organization for the propagation of ophthalmologic knowledge for the mutual benefit of a major section of the physicians of the United States. It occurred to Dr. Gradle that the facilities of the government could be utilized to provide the services of a centralized standardized department of eye pathology for all the academically unattached ophthalmologists of the United States. The specimens sent in by these

HARRY SEARLS GRADLE, M.D.
1883-1950

ophthalmologists could, in turn, serve to build up a central collection of pathological eye specimens, which would be of educational value.

Dr. Gradle's idea was well received by the Army authorities, and, with the financial help of the American Academy of Ophthalmology and Otolaryngology, a registry of pathology, specifically intended for eye pathology, was established as a part of the Army Medical Museum in Washington, D. C.

It appears that Dr. Gradle himself did not feel that he had completed his *Lehrjahre* until after he had returned to Chicago in 1919

and settled down to the practice of ophthalmology in his private office, in the eye clinic of Cook County Hospital and to teaching and research at Michael Reese Hospital, as well as at the University of Illinois, with which he was connected from 1921 to 1927. From 1928 to 1943 he held the position of professor of ophthalmology at Northwestern University Medical School, from which he resigned on July 1, 1943, when the Illinois Eye and Ear Infirmary, of which he had been chief of staff since 1933, became officially a department of the University of Illinois. In the capacity of chief of staff and professor of ophthalmology, he continued to serve until he became incapacitated in the fall of 1945.

Dr. Gradle's greatest gift, bestowed on him by nature, undoubtedly was his faculty to understand people and to recognize, almost at the first glance, their abilities, motives and problems. The way in which this knowledge came to him, unsought, effortless, intuitive, made him a genuine friend of the people. This capacity gave him a deep feeling of satisfaction and happiness about life in this world, which, to a large measure, must have been the reason for his sunny, genial nature and his unfailing sense of humor, which his friends will never forget.

Nature had also endowed him with a rare intellect, a striking keenness of comprehension and a sound, useful, practical originality. The keenness of his mind was well balanced by his understanding of and deep feeling for his fellow men, which accounted for his success as a professional leader and promoter, in which capacity he never left his associates far behind or ever let them feel his intellectual superiority.

Of Dr. Gradle's acquired qualities, his almost encyclopedic knowledge of ophthalmology should be listed in first place. There are very few chapters in this steadily expanding specialty of which Harry Gradle did not have a profound understanding or to which he did not make a valuable contribution. He was an outstanding, but at the same time conservative, surgeon, whose perfect coordination of eyes, hands and mind has been admired by his many students and the thousands of visitors to his surgical clinics. The question of which of his many teachers influenced him most profoundly is difficult to answer because the principle of his own approach to ophthalmology was unification and integration of existing concepts. Anton Elschnig probably left a deeper imprint on Harry Gradle than any other ophthalmologist with whom he studied.

He was a lucid and inspiring speaker and writer, very much in demand as lecturer, moderator and discusser at medical meetings. His knowledge of several foreign languages enabled him to make significant appearances at medical meetings abroad and in South America. As his major accomplishments could be listed his more than 160 contributions to the ophthalmologic literature, in the form of individual articles, sections of textbooks, manuals, lectures and book reviews. Valuable

and informative as these literary contributions have been, there can be no doubt that his foremost accomplishments were not literary and are only very inadequately recorded in his writings. These contributions were (*a*) the organization of the Section on Instruction of the American Academy of Ophthalmology and Otolaryngology; (*b*) the organization of the trachoma clinics in Southern Illinois; (c) the reorganization of the Illinois Eye and Ear Infirmary and its incorporation under the University of Illinois; (*d*) the organization of the Home Study Courses of the Academy of Ophthalmology and Otolaryngology, and (*e*) the founding, together with Moacyr Alvaro, of the Pan-American Congress of Ophthalmology.

These organizations, their purposes and ideals, their effectiveness and usefulness, serve better than the most eloquent words to characterize Harry Gradle and to build an eternal, indestructible monument to a man who all his life did more for people than he permitted people to do for him.

He understood the art of combining the most exhausting professional life with an active family and social life and with culture and recreational activities, in which modern literature, music, travel and golf were most prominent.

Throughout his professional life he was blessed in having at his side a loving, understanding companion to share with him the terrific burdens and responsibilities, but also the immense success, of his career. From 1906 to 1944 this companion was Alice Gradle, the former Alice Perry, a college sweetheart, who rose with Harry to the very top of his professional life, but was called into another world without warning on Oct. 5, 1944. From the abyss of ensuing loneliness Harry did not seem to be able to rescue himself. When the first signs of his heart ailment became manifest, during the early part of 1945, his friends became worried about his physical and emotional status. There an angel stepped in, in the person of Audrey Hayden, who had been working with him as executive secretary of the Illinois Society for the Prevention of Blindness for over 15 years and who, in the spring of 1945, became his wife. It was chiefly her devoted, self-sacrificing and inspiring companionship that made it possible for Dr. Gradle to endure the many hardships of his illness.

The world has lost an outstanding promoter and most successful coordinator in the field of ophthalmology. His spirit survives in the organizations which he has created or fostered and in his many ophthalmologic descendants whom he has started on the right road to a useful and happy professional life.

PETER C. KRONFELD.

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Alfred Cowan, M.D., Chairman pro tem

M. Luther Kauffman, M.D., Clerk

Regular Meeting, March 17, 1949

Treatment of Giant Follicular Lymphoma with Nitrogen Mustard (methyl-bis-[2-chloroethyl]-amine): Report of a Case. DR. BENJAMIN M. CHAMBERS (by invitation).

This paper was published in the March 1950 issue of the ARCHIVES, page 520.

DISCUSSION

DR. LAWRENCE H. BEIZER: Several points are raised by this case. One concerns diagnosis, another therapy and the third prognosis. In this case an adequate biopsy was essential. Once it was found that the lesion was one of the lymphoblastoma group, the exact division of the group did not matter much in the planning of therapy, since it is practically impossible to predict in an individual case what the response will be, regardless of the type of tumor.

The agents used in treating the tumors of the lymphoblastoma group are radiation and the newer chemotherapeutic agents. Roentgen radiation has been used for the longest period. When the lesion is localized, other forms of radiation are often employed, for example, radium or radon. Of the chemotherapeutic agents, radioactive phosphorus and nitrogen mustard (methyl-*bis*-[2-chloroethyl]-amine hydrochloride) have had the longest trial. Others still in the process of investigation are urethan, folic acid antagonists and the bacterial polysaccharides.

Urethan cannot be used satisfactorily in cases in which the leukocyte count is not increased because of its depressing action on the bone marrow, which may at times be extreme. Aminopyrine is the best known of the folic acid antagonists. Its greater value has been in the temporary control of acute leukemias in children. It has not yet had an adequate trial in treatment of the lymphomas. The bacterial polysaccharide which has been given a trial in these cases is the one known as P5; it is related to Coley's toxin.

The chemotherapeutic agent which has proved most effective in the hands of most investigators is nitrogen mustard. Ordinarily, it has been reserved for cases in which roentgen radiation has already been used and in which the patient has become radioresistant. There are occasional cases in which nitrogen mustard is used in preference to roentgen radiation. These are cases in which the lymphomatous process is so widespread that it is hardly possible to treat the patient adequately with roentgen rays. The case presented is an instance in which nitrogen mustard was used in preference to roentgen radiation because it was

felt that roentgen rays might do harm. This case is a particularly good example of the satisfactory use of this agent. The case is, I think, unique, and it is also of importance in that it demonstrates that nitrogen mustard is effective in treatment of this particular member of the lymphoblastoma group. Previously it was thought that good results were obtained only in treatment of Hodgkin's disease. It will be of considerable interest to follow this patient and see how long a remission will be obtained. In the past it was thought that only short remissions were obtained with nitrogen mustard, but in this case I think there will probably be a rather long remission.

Dr. Edmund B. Spaeth: It is to be regretted that Dr. DeLong could not be here this evening. He wished to emphasize two or three points of interest. The first is the life expectancy of patients with this tumor, as illustrated by Mallory's series. It is from six to eight years only. Another point, in the relation of lymphoma to Hodgkin's disease, is the satisfactory response to radium in the former and the absence of response in the latter. I hope Dr. Beizer will comment on this. In Mallory's series 25 per cent died of Hodgkin's disease. None of them, however, showed any sign of Hodgkin's disease until late in the course of their illness.

Dr. Lawrence H. Beizer: A great deal of interest has centered on the relation of lymphomas to Hodgkin's disease. Dr. Custard had an interesting opportunity to study this during the war. He examined all the tissues of patients with diseases of blood-forming organs, and he was able to follow cases in which the original diagnosis of a member of the lymphoma group had been made. As a result of subsequent biopsies and necropsies, he pointed out, as has been noted in the past, that frequently when the original biopsy diagnosis was, for example, giant follicular lymphoma, subsequent biopsies disclosed either lymphosarcoma or Hodgkin's disease, and that in some instances the reverse was true. In some of the cases he studied there had been no treatment; so the change could not have been due to therapy.

In regard to Dr. Spaeth's point, in most cases of giant follicular lymphoma the response to roentgen therapy is rapid and excellent, and a long remission is obtained. On the other hand, it is only occasionally that a long remission occurs in a case of Hodgkin's disease, but there are cases on record in which the patient has had a remission of many years' duration. This only adds to the confusion; histologically one cannot see any difference but clinically the reactions in individual cases may be very different. This has led some workers to group these cases together and to discard the differentiations based on histologic appearance alone. Enough evidence has not yet been accumulated to show that there is no difference between the various members of the lymphoma group; one can make an estimate of the prognosis from the histologic picture but cannot be very accurate in an individual case.

Dr. I. S. Tassman: I should like to present a case from the medical service of the Mount Sinai Hospital which I have had an opportunity to observe during the past month and in which the pathologic diagnosis at biopsy was lymphosarcoma. The case is very similar to the one Dr. Chambers presented. Treatment was also with nitrogen mustard, and apparently the condition has continued to improve.

(Slide) The photograph shows the rather striking ptosis on the left side with a pronounced preauricular adenopathy, and the moderate ptosis on the right side. As I understand it, the effect of the nitrogen mustard is to depress the bone marrow and thus to bring about improvement, perhaps temporary. The orbital condition was a metastatic involvement, particularly on the left side, with a considerable infiltration of the lids, easily distinguishable on palpation.

I believe that nitrogen mustard has been employed in cases of diseases of the lid of a leukemic nature and of some of the other blood dyscrasias. I think that the improvement in these cases has been a temporary remission. The final prognosis, however, is very unfavorable.

Goniotomy in Treatment of Congenital Glaucoma. DR. HAROLD G. SCHEIE.

This paper was published in the September 1949 issue of the ARCHIVES, page 266.

DISCUSSION

DR. P. R. MCDONALD: Through the courtesy of Dr. Shipman, I was able to perform seven goniotomies in his service at Wills Hospital last year. The results were not quite so good as Dr. Scheie's. Seven operations were performed on four eyes. The first patient had had two previous filtering operations on each eye. In one eye the disease was well advanced, and two goniotomies did not control the tension. The other eye has remained free from photophobia, and the patient apparently sees fairly well. Another patient was operated on nine months ago and has done well. The last patient to be operated on had a massive hyphema; this gradually subsided, and the tension is lowered, though it is too early to be certain of the result.

I should like to ask Dr. Scheie why he used atropine after operation and whether, if hemorrhage follows the operation, he ever uses a miotic instead of a mydriatic.

DR. EDMUND B. SPAETH: Dr. Scheie's results are beautiful. I wonder, however, why he does not use the contact lens. I have used it regularly and do not operate without it. Cordes called my attention to a nice point in the use of the contact lens so that reoperations can be done and, at the same time, one can have a fresh area in the angle for incision. This consists in the rotation of the eye slightly nasally or temporally with two fixation forceps. During the first goniotomy the vertical meridian is to lie, let us say, nasally and with the second, temporally, so that three fourths of the angle is available for surgical procedure.

Of the patients whom we have had at the Graduate Hospital, none was operated on who had had surgical treatment prior to the goniotomy. Our failures also were failures with diathermy, with fistulizing operations and with cyclodialysis. Of all the patients operated on prior to goniotomy only two still have vision. One of them, a woman aged 20, still has one eye, with 6/12 vision, a recovery from four operations. The other, also a young woman, has had three operations on the right eye and four on the left with cyclodialysis. She is now a senior in high school and still has 6/30 vision. It is wonderful that she could have this period for education, but the final result is still very much in doubt.

DR. WARREN S. REESE: I should like to ask Dr. Scheie why he could not introduce the air through the goniotomy wound.

DR. WILLIAM ZENTMAYER: Because of the rather favorable results reported at this meeting, it might be of interest to the section to know the hopeless attitude of ophthalmologists toward this condition some thirty or fifty years ago. I sent out a questionnaire to members of the profession and received 25 replies. Only one had any suggestion for the treatment of this condition; and that was Dr. John E. Weeks, who suggested that the new operation of corneal trephining might be of use. I remember the reply made by one of the most skilful ophthalmic surgeons, the late Webster Fox, to the effect that treatment for congenital glaucoma was enucleation of the eye.

DR. I. S. TASSMAN: Dr. Scheie should be congratulated on this presentation, especially since it is an important and necessary advance in the treatment of infantile glaucoma.

I should like to recall three patients whom I have had under observation for six years. These children, with both eyes affected, came to my attention at the age of 1 year, one I think at the age of 10 months. They were presented here about four years ago. All six eyes were operated on—one eye of each patient with an Elliot trephination and the other eye with a modified Lagrange operation. All three patients have been under observation since. They are now about 7 years of age. The eye on which the Lagrange operation was done was lost in each case, but the patients have vision in the other eye which enables them to go about without assistance, although all of them, I believe, are in schools for the blind. The intraocular tension in the better eye remained stationary.

DR. HAROLD G. SCHEIE: Dr. McDonald asked why atropine is used after operation. It has been our practice to use atropine only if the eyes show rather intense ciliary injection during the postoperative course. Once the chamber is formed, there seems to be little danger of promoting the formation of peripheral anterior synechia by its use, because the angles are usually wide open in this type of glaucoma. Management of hemorrhage in the anterior chamber has offered no serious problem in this group of patients. It has been my practice to treat traumatic hyphema with rest and cold compresses. I ordinarily use neither miotics nor mydriatics, although at times there might be an indication for one or the other, as Rychener brought out in his excellent paper on the treatment of traumatic hyphema, given before the Section on Ophthalmology of the American Medical Association in 1943 (*J. A. M. A.* **126:** 763 [Nov. 18] 1944).

Dr. Spaeth has asked why I do not use a contact lens. It is cumbersome, makes the operation much more difficult and in our hands seems to offer no advantage. Furthermore, the cornea in these patients is somewhat hazy, and visualization of the angle is difficult.

Dr. Reese inquired as to my reasons for not injecting air through the goniotomy puncture. The difficulty is that the air will not stay in because the incision cannot be made sufficiently oblique to act as a valve. I therefore use the method described by Chandler, in which a very oblique puncture through the cornea is made with a knife needle. A fine

hypodermic needle is then inserted into the tract, but not into the anterior chamber, and air is injected. The inner lips of the incision act as a valve, preventing the escape of air. The small goniotomy puncture automatically closes as the air enters the chamber.

Enucleations and Implants. Dr. Patrick J. Kennedy and Dr. James S. Shipman.

Forty-five eyes were enucleated or eviscerated, 19 for trauma, 16 for sarcoma, 2 for glioma and 18 for other ocular lesions. Of the patients in the trauma group, only one wore glasses.

There were 10 simple enucleations, 18 buried implants and 17 exposed implants. All the buried implants are still in place. Of the 17 exposed implants, three were lost, in patients aged 4, 10 and 16 years, respectively.

The exposed implants have the advantages over the buried type of better motility and less depression of the upper lid, with less narrowing of the palpebral fissure. On the other hand, the surgical procedure is more difficult, the exposed implant is more likely to be extruded and the cost is greater.

Lantern slides and seven minute motion pictures showing motility of buried and exposed implants and prostheses were shown.

DISCUSSION

Dr. James S. Shipman: Dr. Kennedy is to be congratulated on this excellent presentation. He has been most generous to include me as co-author. Indeed, I have had nothing to do with this fine piece of work except to consent to Dr. Kennedy's doing these new implants on a number of patients in my service at the Wills Hospital. As a matter of fact, I have been rather critical and skeptical of the whole affair.

I have been using the Dimitry or the Frost-Lang type of implant, which is completely buried, for so long that it has been difficult for me to see how a partially buried implant would stay in. I had always felt that when the implant became visible it was a sure sign that the implant, whether gold, plastic or glass, was coming out. If the implant was bone, it would become irritative and have to be removed, and this often proved to be a major procedure.

These newer types of implants are only partially buried, with a considerable portion of the anterior surface exposed, and for this reason I have felt that the implant would not stay in. In this type of implant it would appear that one is subjecting the scleral cup and Tenon's capsule to infection. However, something seems to take place which cannot be explained and which does not occur with the older, buried implant when it becomes partially exposed.

I have become interested in this newer procedure, as described by Dr. Kennedy, and I have been convinced that we should at least give it a trial. I have operated in one case by the transscleral route; the implant, a Cutler universal type, was inserted in the scleral cup with the muscles still attached. I chose this type of implant because it more closely approaches the Dimitry type. Dr. Kennedy assisted me in doing this operation; the whole procedure was very simple, and no complica-

tions were encountered. The hemorrhage was controlled by first clamping the optic nerve with a hemostat before cutting it. The patient's postoperative recovery was uneventful, except that the reaction was slightly greater than usual, according to Dr. Kennedy. About two weeks after the patient was discharged from the hospital the implant came out through the opening in the front of the scleral cup. This was one of the cases mentioned by Dr. Kennedy.

Notwithstanding this unfortunate experience with my first case, I feel that this type of implant, namely, the intrascleral, is the most logical and that, when the last word is said on partially buried implants, this type, or one similar to it, with the implant in the scleral cup, to which the rectus muscles are still attached, will be the one of choice. I certainly intend to try more implants of this type, and I am grateful to Dr. Kennedy for encouraging and stimulating me in this work.

I feel that too many simple enucleations and disfigured sockets with poorly fitting prostheses are due to the fact that the surgeon was not industrious enough or thoughtful enough at least to try some type of implant. As surgeons, we owe it to our patients to give them the best-looking prosthesis possible, and we should all give these newer procedures a trial. If the method fails, we have done no harm, and the socket is no worse than if it had not been tried.

DR. P. ROBB MCDONALD: In 1886 Frost first reported the implantation of a foreign substance into Tenon's capsule. From then until the present decade modifications of the enucleation and evisceration procedures have consisted essentially of changes in the various implant materials. With the advent of World War II and the shortage of suitable glass prostheses, attention was directed to the use of plastic material. All ophthalmologists owe a debt of gratitude to Drs. Ruedemann and Cutler, who were the pioneers in developing the integrated implants.

Dr. Kennedy has discussed the advantages and disadvantages of the semiburied implants. The operative procedure is not difficult, and in an uncomplicated case it takes little, if any, more time than the classic Dimitry operation. The results, in my opinion, are unequivocal, and, as the motion picture has shown, it is difficult at times to tell which eye has been enucleated. In every case in which I have operated the patient considers his prosthesis cosmetically more acceptable than his former blind eye. In two of my cases the enucleation had been performed 10 and 15 years previously. An exposed bone ball was removed from the sclera in one and a gold ball from the floor of the orbit in the other. The placing of an integrated implant as a secondary operation is time consuming, but the results are worth the effort.

One of the criticisms of this procedure is the exposure of a foreign body in the orbit. Surgically, this would appear unsound. However, I have not as yet seen any cases of secondary infection. In fact, it is amazing how little reaction occurs once the initial postoperative period is over. I have a patient whose prosthesis is removed only once every two or three weeks. At this time it is washed with soap and water and replaced.

There is an interesting feature about some of these patients: Prior to operation the blind eye is frequently exotropic, and convergence, if

accomplished, is very poor; after operation, however, the eyes may converge rather well.

CAPT. C. L. SETTEMBRINI, New York: Since May 1948 the staff of the ophthalmology department at Valley Forge General Hospital have performed 24 enucleations. In 22 the Cutler universal motility implant was used. A combined evisceration and enucleation has been done in 17 cases; enucleation with insertion of the Cutler implant in Tenon's space, in 4 cases, and reimplantation in an orbit in which an implant had not been previously placed and the simple enucleation had been performed about a year prior to the patient's arrival at Valley Forge General Hospital, in 1 case.

We have been able to observe each of these 22 patients for four weeks or more, and we have had only one complication—extrusion of the implant after a period of seven months. The patient was hospitalized during that period, for administrative reasons. He received a blow to the orbit, cellulitis developed and the implant was extruded gradually. We finally had to excise it.

I have pictures from some of the more recent cases which I should like to show (moving pictures).

DR. NORMAN CUTLER, Wilmington, D. C.: I have known about Dr. Kennedy's work. I obtained one of his implants through Dr. McDonald.

There is a characteristic of an ideal implant that Dr. Kennedy might add to his list; that is permanence. The question of permanence has not yet been answered, and probably will not be for some time.

I was glad to hear Dr. Shipman speak out in favor of using some of the recent types of implants, despite his unfortunate experience. Even if these implants eventually prove to be unsuccessful, they may lead to something better than we have had; at least during that interval the patient is happy with the result.

In connection with the extrusion through the corneal opening, like Dr. McDonald, I thought it could not happen. I know of two or three other cases in which it has happened. Just why, I do not know; apparently, the sclera stretches. I believe it will be possible to replace the implant at the time of extrusion. I say this because within the last two months I have had a patient who had been hit with a golf ball a month or so previously, with severe laceration of the sclera. The eye had then begun to shrink, and I carried out an evisceration procedure. The laceration extended pretty well across the cornea, through the sclera and about 10 mm. through the external rectus muscle. In order to excise all the scar tissue, I had to open the scleral collar completely, remove some of it and then resuture it. When the patient went home, the implant looked just as well as any other. In addition, a physician, about a year ago, put in an implant by eviscerating the contents of the globe, making an incision from front to back, putting in an implant and suturing it. It is still in place, and quite satisfactory. In the cases in which the implant has extruded there has been no proliferation of scleral tissue. There has been proliferation of tissue from the anterior scleral collar. In regard to the sutures, the scleral type of implant can be put in without any sutures at all.

I have used the ball and mesh implant as an enucleation procedure, with only four absorbable surgical sutures through the muscles and through Tenon's capsule and the conjunctiva.

I feel that Ruedemann is really the person who deserves all the credit for attracting attention to the possibilities of putting in an incompletely buried implant. In my opinion, the most movement is obtained from the evisceration procedure and the next from the enucleation procedure.

DR. JOSEPH WALDMAN: What would happen to a patient with partially embedded implant if an acute purulent conjunctivitis should develop? I do not mean immediately after operation, but later. What assurance can we give the patient that there is no danger aside from extrusion of the implant, should an acute infection occur?

DR. JOHN FINDLEY, Altoona, Pa.: I should like to ask Dr. Kennedy how many cases of chronic low grade conjunctivitis he sees with this prosthesis. It seems to me that the irritation caused by this prosthesis might be considerably severer than that caused by the ordinary type.

DR. PATRICK J. KENNEDY: We do not feel that conjunctivitis is any more of a hazard with an exposed implant than with a buried implant. The acute conjunctivitis responds very well to penicillin or sodium sulfacetimide. The chronic conjunctivitis is taken care of by frequent irrigations of nitromersol N. F. (metaphen®); 1:10,000, or other mild antiseptic solutions. The socket with an exposed implant needs no special care. It should be irrigated at least twice a day with water and the prosthesis cleaned with soap and water. Some patients are allergic to plastics. These will produce more reaction, and the increased amount of mucoid discharge will necessitate frequent cleansing of the socket. We are still hoping to find a nonallergenic plastic material.

Meningitis following panophthalmitis is still mentioned in textbooks but is so rare that few in this gathering have ever seen it. Meningitis as a result of infection in a socket is a rare possibility. The advent of the exposed implant should not increase the hazard of meningitis, since the implant is surrounded posteriorly by viable tissue, possessed of the same immune properties as those of other body tissues. It is possible that a retroimplant abscess might occur, but, again, it is most unlikely. Time will tell whether these conditions are to be feared.

Perce DeLong, M.D., Chairman

M. Luther Kauffman, M.D., Clerk

Regular Meeting, Dec. 15, 1949

Thyrotropic Exophthalmos and Pseudotumor: Report of a Case. DR. EDMUND B. SPAETH and DR. HOWARD BEDROSSIAN (by invitation).

The literature was reviewed, and Means's theory of the mechanism of thyrotropic exophthalmos was discussed. Mulvany's theory of different mechanisms producing thyrotoxic and thyrotropic exophthalmos

was next discussed, and pathological evidence supporting this theory was presented. A clinical and pathological comparison was made of thyrotoxic and thyrotropic exophthalmos. An interesting case of thyrotropic exophthalmos with a pathological report was presented.

DISCUSSION

DR. ROBERT GROFF: My remarks will be concerned with the procedure of decompression of the orbit.

In the present case the right orbit was explored through an extracranial approach. Because the exposure was inadequate, a misinterpretation of tumor tissue was made, and for this reason roentgen therapy was given. Because of the intensity of the roentgen radiation the eye became blind and had to be removed. Had the orbital contents been explored by means of an intracranial approach, I am sure this mistake would not have been made, roentgen therapy would not have been given and the eye, in all probability, would have been saved.

The intracranial approach in exploration of the orbital contents for exophthalmos has three distinct advantages. First, it permits exploration of the sphenoidal ridge. This is extremely important, because the inner side of the sphenoidal ridge is a common site for the development of meningioma. This tumor is a common cause of unilateral exophthalmos, but invariably it is associated with a thickening of the bone, which can be demonstrated in the roentgenogram. Second, after the roof of the orbit has been removed, the orbital contents can be clearly seen and therefore carefully examined. Thus, one can determine whether there is a tumor present or whether the pathologic process is diffuse, involving the entire contents of the orbit. Third, if a tumor is not found on the sphenoidal ridge and no pathologic condition is found in the orbit itself, exploration for an aneurysm of the internal carotid artery may be made. It may be seen, therefore, that the intracranial exploration of the orbit can rule out three types of lesions, two of which are not within the orbit itself.

In the case under discussion two features were unusual. First, the roof of the orbit was extremely thick, necessitating use of a hammer and chisel in order to obtain an opening so that the bone could be removed. Because of this factor, it is apparent that an attempt to explore the orbit through a lateral approach would have been almost impossible. Second, when the bone flap was raised, the dura, which was densely adherent to the bone, was torn. Ordinarily, the dura would not have been opened, the entire procedure being done extradurally; but in this instance we were in the intracranial cavity before we intended. The situation presented no particular problem, but I am sure it was responsible for the period of aphasia following operation, since more traction had to be made on the frontal lobe than would have been had the dura remained intact. It is important when one is operating on the dominant hemisphere that the patient be informed before operation that there is a possibility of his becoming aphasic. By so informing the patient, one prevents the anxiety which occurs after operation when the patient learns that he cannot talk.

The intracranial decompression of the orbit should be looked on as the ideal approach to intraorbital lesions. The procedure is simple,

is not attended with particular shock and takes only one to two hours to performed. I recommend it enthusiastically.

DR. EDMUND B. SPAETH: This case is one in which it is easy to be critical and difficult to be restrained.

The first fault was in making a diagnosis of orbital tumor and in proceeding with roentgen therapy without any attempt being made to confirm that diagnosis. One cannot make a diagnosis of an orbital tumor which might respond to roentgen therapy on roentgenologic evidence alone.

After the development of the exophthalmos of the left eye, the slides of tissue from the right orbit were sent to various pathologists for reexamination. Pseudotumor had been the original diagnosis. At the time too little attention was paid to microscopic examination of the muscles as these were found in sections from the orbitotomy. This omission was the second mistake. The third was the reconsideration of possible intracranial aneurysm. This case demonstrates beautifully one of Walsh's subdivisions in his classification of aneurysms with complete external ophthalmoplegia. It was because such an aneurysm was suspected that the arteriogram was made. Even at that, the correct or most probable diagnosis was made not by a pathologist, but by a neurologist.

DR. C. E. G. SHANNON: Three years ago I had the privilege of presenting before the section of ophthalmology of the Medical Society of the State of Pennsylvania five cases of exophthalmos of thyropituitary origin. Four of the patients, in the late thirties, were admitted to Jefferson Medical College Hospital with a diagnosis of thyrotoxicosis. Operation was advised and was carried out successfully. Unfortunately, ocular palsies had developed. At that time I was particularly interested in that phase of the subject. About a year after the operation I carried out procedures for correction of these muscular palsies, and I am happy to report that the results were gratifying. In two of the cases I succeeded in securing single binocular vision. In the third case, which was seen by Dr. Zentmayer, after the muscle operation the eyeball surprisingly returned to its normal position—a development for which I can offer no explanation.

At present, I am particularly interested in the fifth case, of malignant exophthalmos, and I should like to read a brief history.

A man aged 46, a mechanic, when seen in August 1943, complained of nervousness, loss of weight, excessive sweating and pronounced exophthalmos. He was admitted to Pennsylvania Hospital in October with all the features of thyrotoxicosis and with a basal metabolic rate of 126 per cent. On October 22 an almost total thyroidectomy was performed, revealing diffuse toxic hyperplasia of the gland. However, the exophthalmos and nervousness gradually increased, and on Jan. 1, 1944 there was sudden marked proptosis, followed by photophobia, diminished visual acuity and supraorbital pain. He was admitted to Jefferson Medical College Hospital on January 21, with typical bilateral malignant exophthalmos and advanced keratitis, so that vision was totally lost temporarily in the right eye. The basal metabolic rate was —21 per cent. On January 22 scarification of the conjunctivas was done on both sides to relieve chemosis and eye shields were applied as a protective measure. On January 27 the right eyelids were sutured, but this procedure also proved ineffective. On March 9 Dr. Rudolph Jaeger per-

formed a Naffziger operation on the right side and a Naffziger-Krönlein operation on the left side. Continuous administration of thyroid and a moderate course of irradiation to the pituitary gland were carried out. The patient was discharged on May 18.

(A moving picture of the operation performed by Dr. Jaeger was shown.) The point of paramount importance in this case is whether the condition was thyrotropic or thyrotoxic hyperthyroidism.

DR. WILLIAM T. HUNT JR.: An interesting test has been devised by Dr. Savino D'Angelo of the staff of Jefferson Medical College. When tadpoles of the leopard frog were starved, they remained in a state of stasis as long as 30 days. Examination showed the thyroid epithelium to be atrophic, the gland distended with colloid and no hindlimb growth. Injection of 0.05 cc. of thyrotropic hormone into the peritoneal cavity produced a certain amount of growth of the hindlimbs and a certain increase in the height of the thyroid epithelium. The effect of as little as 0.0005 Junkmann-Schoeller unit could be detected (*Endocrinology* **46:** 39-54 [Jan.] 1950). The ratio of the height of epithelial growth to the length of growth of the hindlegs when the frog was stimulated by thyrotropic hormone has been determined. Thyroxin will cause growth of the hindlegs, but it does not increase the height of the thyroid epithelium. On the basis of these findings, a test has been devised to ascertain the approximate amount of the thyroxin and thyrotropic hormone in the raw blood serum. Standards have been set up. Serums from pathological and normal patients have been used. The test gives an idea of the abnormal ratio associated with endocrinopathies and may serve as an adjunct in the diagnosis and therapy of thyropituitary dysfunction.

Observations on Retrolental Fibroplasia. DR. WILLIAM O. LA MOTTE JR., Wilmington, Del., and DR. GEORGE S. TYNER (by invitation).

The literature on retrolental fibroplasia was briefly reviewed, with particular reference to the opposing views of a congenital origin versus a postnatal acquired disease. Mention was made of the evidence in the recent literature against any relation of the incidence of the disease to such factors as increased survival rate, maternal disease and infant management and feeding.

Cases were presented from the Delaware Hospital, in Wilmington, and from the Hospital of the University of Pennsylvania which seem to indicate an increased incidence of the disease in recent years and to confirm the view that increased survival rate, maternal disease and infant feeding are factors of no demonstrable significance. The infants examined periodically from birth showed no clinical evidence of the disease at the time of the first examination, and the disease developed according to the pattern first described by Drs. Owens. A primarily retinal disease, with vascular engorgement and tortuosity, retinal exudative phenomena and retinal detachment, constituted the picture invariably seen. The first retinal changes were observed as early as 23 days of age and as late as 45 days. In no infant whose fundus appeared ophthalmoscopically normal on discharge from the hospital has the disease developed subsequently. During 1949 the disease has developed in nine of 18 infants weighing less than 4 pounds (1,814 Gm.) at birth,

and the incidence has been just as great in the 3 to 4 pounds (1,307 to 1,814 Gm.) group as in the infants weighing under 3 pounds.

Two infants were observed whose eyes were normal at the time of the first examination except for extreme, threadlike attenuation of all the retinal vessels. These vessels subsequently assumed a normal caliber, and then there developed the striking vascular and exudative picture typical of the disease. The possible significance of these attenuated vessels was speculated on.

The results of the use of alpha tocopherol acetate prophylactically and therapeutically were recorded. In two cases in which the striking vascular stage of the disease had developed the eyes returned to normal during vitamin E therapy. This observation is considered of possible significance because prior to the use of vitamin E no eye in which the disease had reached the vascular stage returned to normal. In a control group of 11 infants weighing between 3 and 5 pounds (1,307 and 2,268 Gm.) at birth, only one exhibited the disease, and then only the marked vascular stage without exudate or detachment, changes which reverted to normal during vitamin E therapy started at the age of 26 days. In a similar group of 17 infants who were on vitamin E therapy from shortly after birth, three have acquired the disease bilaterally in its severest form, despite adequate vitamin E levels in the serum.

The failure of prophylactic administration of vitamin E from shortly after birth to prevent the development of the disease was emphasized. The possibility that this vitamin supplement might even be harmful was suggested.

DISCUSSION

DR. GEORGE S. TYNER: The eyes of all infants in the premature nursery of the Hospital of the University of Pennsylvania are examined as soon after birth as conditions permit. Those with birth weights of 4 pounds or less are examined at weekly intervals while in the nursery. Those with birth weights over 4 pounds are examined less frequently. During the past five months, 42 premature infants have been observed. Ten weighed less than 4 pounds at birth, and the disease was found in two of these infants. Both were boys, and both had a normal female twin. Neither infant has any other significant abnormality. The earliest sign of the disease was present at the time of the initial examination.

CASE 1.—J. F., with a birth weight of 1,795 Gm., was first examined 15 days after birth. At this time both eyes showed extremely dilated and tortuous retinal veins and arteries, the right eye being the more affected. In addition, the right eye showed remnants of a persistent anterior pupillary membrane. There was gradual progression in the size and tortuosity of the vessels during the next two weeks, after which no significant change was observed for one month. If anything, there was slight improvement in the appearance of the fundi. After this quiescent period, bilateral retinal detachments were noted in the periphery, the right eye being the more affected. The right disk was blurred in outline and partially obscured by what may have been new-formed fibrous tissue. The detached retina resembled retinitis proliferans, with fibrous bands extending forward into the vitreous. Vascular proliferation appeared on the surface of the retina. No hemorrhage was noted. This child has received 150 mg. of a water-miscible preparation of vitamin E daily since the third week of life. The vitamin

E level of the blood, determined by Dr. Paul Goldhaber of Harvard Medical School, was 4.74 mg. per 100 cc. (normal value 0.2 mg. per 100 cc.).

Case 2.—M. H., with a birth weight of about 3 pounds (1,350 Gm.), was first examined 52 days after birth. At this time the eyes were normal except for a single dilated retinal vein in the left eye. Over a period of one month following the initial examination, progressive enlargement and tortuosity of the retinal vessels were observed. This change became bilateral and involved all the retinal vessels. Two months after the initial examination, bilateral symmetrical changes were noted on the disks, extending temporally. The appearance of these changes most resembled the condition known as congenital retinal septums or folds. This child has also received high doses of vitamin E since the progressive vascular changes were first noted. The preparation used in this case was an oily form of vitamin E. The blood level was found to be 0.57 mg. per 100 cc.; although within normal range, this value was only about one-tenth that of the child receiving the water-miscible preparation. As soon as this lower level was noted, the child was also placed under treatment with the water-miscible preparation.

The number of premature infants examined periodically from birth is too small to permit the drawing of any conclusions. It is apparent, however, that early and frequent examinations must be made on all premature infants with birth weights of 4 pounds and less. As pointed out by Dr. La Motte, the disease process occurs with increased frequency in children with birth weights near the 4 pound level, as well as in the extremely small infants. The condition has been noted much earlier than the present literature indicates. The progression of the disease process, despite early administration of vitamin E, is impressive.

Dr. I. S. Tassman: In the study of these cases both speakers have had an excellent opportunity to clear up several points that have heretofore been in dispute. I should like to ask whether they have seen any cases which resembled those described by Reese (Persistence and Hyperplasia of Primary Vitreous: Retrolental Fibroplasia—Two Entities, Arch. Ophth. **41**: 527 [May] 1949), in which the condition might be considered a persistent primary vitreous. Most of the cases described here seem to belong to the category of retrolental fibroplasia as described by Drs. Owens; yet there is a great similarity between the two conditions. Reese, however, recently stated there are two separate conditions: the one, retrolental fibroplasia, and the other, persistent primary vitreous.

The difference appears to be not so much in the appearance of the condition as, rather, in its origin or cause; i. e., in retrolental fibroplasia it appears that the detachment of the retina or the edema of the retina following the changes in the vessels initiates the condition. In other words, retrolental fibroplasia begins posteriorly in the retina with changes in the retinal vessels; then follow edema and detachment; then, cloudy vitreous, and then, band formation, extending forward through the vitreous until the entire posterior surface of the lens is covered.

It appears that the other condition is initiated by a persistent primary vitreous and failure of the secondary vitreous to develop. In other words, it is an interference with the development and regression, leading to fibrous, bandlike formation; from this source the proliferation extends posteriorly toward the retina, and the detachment of the retina is secondary.

Hemorrhages occur in both conditions, but in the case of persistent primary vitreous there are also the remnants of the hyaloid artery and the tunica vasculosa lentis, which are not seen in retrolental fibroplasia.

Were any cases encountered which represented the condition described or which might be considered instances of persistent primary vitreous? Of course, the diagnosis of the latter condition was made by Reese after pathological examination. The diagnosis of retrolental fibroplasia is usually a clinical one.

With regard to the infants treated with alpha tocopherol acetate, or with vitamin E in any form, were any other vitamins given at the same time, or was vitamin E used exclusively? Was vitamin A eliminated entirely from the diet of all these infants? Owens and Owens stated the belief that these premature infants were possibly deprived of vitamin E because of the excessive amount of vitamin A in the diet, since vitamin A will destroy or inhibit the levels of vitamin E. It would be interesting, therefore, to know whether vitamin A was given or whether it was included at all in the diet or in the feeding of these infants.

Dr. M. Luther Kauffman, Jenkintown, Pa.: I have had the opportunity of seeing at one place or another about 18 infants with this disease, the series being equally divided between males and females.

It is obvious to me that the pattern is not always exactly the same. Several times I have been impressed by the appearance of the retinal separation in the periphery without much vascular change; strangely, my general impression is that in cases in which the retina was partly involved the temporal fundus was oftener affected than the nasal fundus and that in several of them the detachment ended in folds running from the disk temporally. It is also obvious from this observation that some of the nomenclature relating to fundus findings may have to be revised. The congenital folds that have been observed in the past may have to be brought into this category.

Most of the patients whom I have seen have been very young, and it is the infants weighing under 3 pounds at birth who have almost universally had the fetal type of vitreous, resembling the vitreous of high myopia. It is difficult to see the fundus. In some of the eyes which have cleared, retrolental fibroplasia has later developed. In some cases the infants appeared normal with a weight of over 5 pounds, and the condition developed after they left the hospital.

I am in entire agreement that retrolental fibroplasia can occur in infants who weigh over 3 pounds or nearly 4 pounds, as well as in those under 3 pounds. In one patient whom I have observed, the disease is confined entirely to one eye; that patient at the time of this report is nearly 8 months old.

Dr. William O. La Motte Jr., Wilmington, Del.: Dr. Tassman has asked whether any of the present cases might not fall in the category of persistent primary vitreous. As far as I know, no one has observed retrolental fibroplasia develop from the vitreous, since it is thought to be present from birth. The only cases in which the disease has been seen to develop from eyes apparently normal at birth have followed variations of the pattern described by Owens and Owens. Reese has stated that the great numbers of cases which had occurred with increasing frequency

are instances of true retrolental fibroplasia, while the entity based on persistence of primary vitreous is relatively rare.

Dr. Tassman inquired about the use of other vitamins in conjunction with vitamin E. Since early reports seemed to point to water-soluble vitamin A as a factor in this disease, this vitamin has been withheld in water-soluble form but supplied in oily form, such as percomorph liver oil, which, of course, also contains vitamin D. Ascorbic acid has been the only other supplement. I have not dwelt on the interrelation of these vitamins, because of the opportunity we shall have next month to hear Dr. V. Everett Kinsey discuss this very subject.

I agree with Dr. Kauffman that one has only begun to explore the varieties and ramifications of this disease, and the sometimes conflicting observations of different investigators only stimulate one to look further.

Reduction in Visual Acuity Due to Excessive Sunlight. Dr. R. H. Peckham (by invitation) and Dr. R. D. Harley, Atlantic City, N. J. (by invitation).

The dark adaptation of the retina occurs when the eye is in darkness or when the level of illumination is very low, as at night. There is also a reverse adaptation phenomenon, that of light adaptation, when the level of the illumination is bright, as during the day or under artificial illumination. The effect of excessive exposure to sunlight was shown by Hecht and associates (*Am. J. Ophth.* **31:** 1573 [Dec.] 1948) to amount to about 0.2 log unit, or to require an increase in absolute threshold, in dark adaptation, of about 150 per cent. Clark and associates (*Am. J. Ophth.* **29:** 828 [July] 1946) confirmed this finding, working also at the extreme level of dark adaptation, and they also showed that sunglasses of 12 per cent transmission served to protect the retina against this loss of sensitivity.

These observations raise two questions: "Is there a loss of retinal sensitivity that is effective in reducing photopic vision?" "If there is such an effect, can it be prevented?"

Such an effect in photopic vision would be expected in the perception of low contrast objects in dim photopic illumination of about 1 to 1/10 foot lambert and could be measured as a reduction of visual acuity at these levels. Blackwell (*J. Optic. Soc. America* **36:** 624, 1946) has published measurements of normal visual acuity at low contrast and dim illumination. The visual acuity under such conditions was measured on 70 lifeguards of the Atlantic City beach patrol during the summer of 1948. It was found that a gradual decrease of visual acuity occurred during the course of the summer. It was also found that the observations were very difficult to make and that large individual differences were found.

It has been pointed out that the critical fusion frequency for a flickering light depends on the brightness of the light (Hecht, S., and Smith, E. L.: *J. Gen. Physiol.* **19:** 979, 1936; Crozier, W. J., and Wolf, E.: Ibid. **24:** 505, 1941). It was reasoned that if the brightness of the light were kept constant, individual differences in critical fusion frequency would represent the effectiveness of the light on the retina—in other words, retinal sensitivity. The critical fusion frequency of a flickering light was determined at various times during the summer of

1949 on a second group of lifeguards at Atlantic City. The measurements were made on these men in the morning and evening of the first three days of beach patrol duty, morning and evening at the end of a week and morning and evening at the end of two months. The 30 lifeguards were divided into three groups. One was provided with dark glass goggles of 10 to 15 per cent transmission; one provided themselves with commercial goggles of 35 to 50 per cent transmission, and one preferred to wear no sunglasses.

The group with special dark sunglasses showed less loss from morning to night and better recovery from night to morning than did the other two groups. The other two groups showed consistent loss of retinal sensitivity, as shown by the critical fusion frequency of flicker, amounting to an average of approximately 0.2 log unit (37 per cent reduction of sensitivity), with individual records not infrequently amounting to 1.0 log unit (90 per cent loss) on various days. This group also showed greater inability to recover retinal sensitivity during the night than did those with special dark sunglasses. These values correspond to the losses in visual acuity at low contrast found the summer before and to the loss of threshold sensitivity reported earlier by Hecht and Clark and their associates.

This loss of sensitivity can be interpreted as a reduction of effective illumination, or as a reduction of visual acuity for low contrast objects. (The reduction also occurs for high contrast objects in bright light, but is less noticeable.) For example, the light from a 60 watt bulb would be only as effective to an exposed subject as that from a 40 watt bulb to a normal person. The effect can be also predicted for the condition of driving an automobile and may be an important contributory factor in traffic accidents.

The loss can be prevented by wearing very dark sunglasses, of about 10 to 15 per cent transmission, as shown by our own experiments and those of Clark and associates (*Am. J. Ophth.* **29:** 828 [July] 1946). The loss cannot be prevented by wearing commercially produced sunglasses of 35 to 50 per cent transmission. Since Clark's sunglasses transmitted infra-red and ultraviolet radiation to a considerable degree, and since the commercial sunglasses, of 35 to 50 per cent transmission, absorbed these rays, it is obvious that the loss is caused by the excessive visual brightness of the sunlight.

DISCUSSION

DR. R. D. HARLEY, Atlantic City, N. J.: Recent published work by several investigators has shown conclusively that the rate of dark adaptation is altered to a large extent by the intensity of the brightness to which the eyes have previously been exposed. It is also known that adaptation to light of high intensity delays not only the onset of rod adaptation but also the final dark adaptation threshold. Independent studies begun four years ago by one of us (R. P.) substantiate these results.

Having been stimulated by these observations, we next turned our attention to consideration of the effects of sunlight on the normal eye of persons light adapted to ordinary intensities. Information available was inadequate to answer our precise question, for we reasoned that

there should be a loss in cone vision comparable to that found for rod vision.

In our experiments the aim was to determine the loss of retinal sensitivity (i. e., the cone portion) in the light-adapted eye, to the exclusion of scotopic vision so far as possible.

In the event that a loss of sensitivity was encountered, we proposed to evaluate the effects of low transmission glasses as an inhibiting mechanism. The methods employed for this determination consisted in the use of contrast discrimination at low photopic brightness levels the first summer and measurements by the flicker apparatus the following summer.

Our findings indicated that loss of sensitivity in exposed eyes begins in three to five hours and is cumulative over a period of seven days. In many subjects recovery took place overnight, while in others the effects were additive for a period of a week, until no further loss was encountered.

Furthermore, our results show that recovery of retinal sensitivity is likely and that the total effects are not permanent. It is to be emphasized that we were not concerned with the effects of direct exposure to the sun or with the question of eclipse blindness.

Ophthalmologists can make use of this information when prescribing for persons anticipating exposure to brightness levels to which they are not accustomed and to which they cannot readily adjust.

The clinical significance of these experiments on the loss of retinal sensitivity as a whole can be appreciated when one considers the effect of reduced visual efficiency for all visual tasks in which illumination is critical, such as in the daily work or in automobile driving under artificial lights.

One might ask what relation exists between visual acuity and perception of flicker. Visual acuity depends on the ability of the eye to resolve two stimuli separated in space, whereas flicker perception entails resolution of two stimuli separated by time. The common denominator of the two processes is retinal sensitivity, and both functions will be influenced by a change in sensitivity. The flicker instrument appears to be a valuable adjunct to the further study of problems dealing with retinal sensitivity.

In conclusion, our investigation shows that loss of sensitivity in the cone portion of the retina occurs from the presence of sunlight and glare under average conditions at the beach. Data obtained by the methods of low contrast discrimination and flicker fusion frequency were comparable. The results indicate, in effect a loss of visual efficiency as compared with vision under ordinary lighting conditions.

DR. ALFRED COWAN: The results of the kind of work being done by Dr. Peckham are of great importance to ophthalmologists. It would be sufficient if it were only to show the utter uselessness of the slightly tinted glasses. Slightly tinted lenses have just as much effect as pieces of cellophane.* On the other hand, the results shown in this paper stress how important it is for sunglasses to be dark.

It was found during the last war that dark glasses which transmitted 12 to 15 per cent of light were not of much use in the arctic, in the tropics or in those places where the light was of extreme intensity. Before the war was over, the men were using glasses with transmissi-

bility of only 4 per cent, and it was found that the Germans were using even darker glasses than that.

It is obvious how little help is offered to persons exposed to high intensities by the ordinary commercial dark glasses, which transmit 25 or 30 per cent of light, and these are fairly dark glasses too, as we see them. Imagine, also, the effect on a person who has been exposed to extreme sunlight all day, and who has lost as much sensitivity as Dr. Peckham has shown, of wearing any kind of dark glasses at night or indoors, even though he has been protected all day long with good dark glasses.

Wilfred Fry, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Regular Meeting, Feb. 16, 1950

Books for the Blind. Dr. Burton Chance.

Dr. Chance presented three books of raised type for use by the blind and gave a brief sketch of the history of the invention of printing of embossed pages.

Roman alphabet and Arabic numerals were the early characters devised, and these were superseded by dots or "points," as arranged by Barbier and later by Braille. These characters consisted of various combinations of six "dots" in forms to be comprehended by pressure by the tips of the fingers. Not all countries use the same arrangement, but it is hoped that the day is not far distant when a universal arrangement can be accepted.

The well known Moon alphabet is still used, especially by adults, and is taught in the schools.

It is the intention of the librarian of the College of Physicians to arrange a classification of books for the blind, and he accepted those offered as the nucleus of the proposed collection, expressing, as they do, three varieties of characters in active use.

Intractable Postoperative Diplopia. Comdr. G. L. Tabor Jr. (MC), U. S. N. (by invitation).

This paper is published in the present issue of the Archives, page 517.

Surgical Principles in Concomitant Convergent Strabismus. Dr. Glen Gregory Gibson.

As a result of some clinical research, a group of principles was formulated. These have been helpful in reducing the incidence of untoward results following surgical procedures for concomitant convergent strabismus of both the primary and the secondary type. Four main questions must be answered before operation: When should the operation be performed? Which muscles should be selected? Which operation should be performed? How much operative correction should be done?

A knowledge of the binocular reflex development in childhood is helpful in attempting to answer these questions. This subject has been discussed by Chavasse and covered by Duke-Elder (Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1949, vol. 4). The

development of visual acuity and ocular movement from birth to the age of 6 years, when those functions have reached normal levels, is most important to evaluate, since the reflex development can be modified during these formative years and cannot be so readily changed after the age of 6.

This variability in early life and invariability in later years makes it necessary to divide cases of esotropia into early and late groups, since the management of the two types is different. An early case is one in which the patient is under 5 years of age and the duration of the esotropia is less than 18 months. Other cases are classified as late.

It is desirable to operate in early cases between the ages of 3 and 4 years, if possible, so that there is still time for the development of binocular vision. Late cases may wait until a convenient time.

The second question, as to the selection of muscles, is important, even though the muscles are not primarily, but are secondarily, involved. This selection necessitates classifying the activity of the four horizontally active rectus muscles as + 1, + 2, + 3 or + 4 or — 1, — 2, — 3 or — 4, in an attempt to estimate the hypertonicity, the contracture or the atony present in each muscle. Rather characteristic rotational groups are encountered, in both the symmetrical and the asymmetrical types, permitting the operative attack to be directed to the two most abnormally acting muscles. This determination of the muscular action will help in deciding whether the operation should be on one muscle of both eyes (usually in cases of alternating squint) or on both muscles of one eye (usually in cases of monocular squint).

In answer to the third question, as to which procedure should be selected, I have had my most gratifying results with bilateral recession in late cases of symmetrical esotropia and with marginal myotomy, as advocated by Chavasse, in the early cases of symmetrical esotropia, provided the symmetry was of both the motor and the sensory type. In cases of asymmetrical esotropia, both late and early, recession of the medial rectus combined with resection of the lateral rectus is preferable.

In answer to the fourth question, as to how much operative correction should be done, graduated amounts of correction are not necessary in early cases, whereas they are indicated in the late cases.

The altered physiological and pathological condition serving as a basis for these statements and the disadvantages, advantages, limitations and objectives of these procedures were discussed.

The chief advantage of this system is the avoidance of postoperative overcorrection. The motor results were 92 per cent satisfactory at the first operation. Even in the early cases only 30 per cent of the patients obtained simultaneous macular perception, and the cause of this was discussed. The importance of the age of the patient, the age of the patient at the onset of the squint and the duration of the condition were reduced to surgical terms. The surgeon must not be dogmatic; his concepts should be as elastic as is the function of the muscles.

DISCUSSION OF PAPERS BY DRS. TABOR AND GIBSON

Dr. William E. Krewson III: It has been suggested that I open the discussion on these two papers together. It is my feeling, however, that, while they are both concerned with ocular muscles, they present entirely different problems.

Dr. Tabor has covered the literature of intractable postoperative diplopia thoroughly and has shown considerable initiative by obtaining personal communications from numerous contemporaries in the field of muscle surgery. He has left little to be said. Fortunately, the condition is quite infrequent. While many patients with strabismus experience transient postoperative diplopia, very few have prolonged postoperative symptoms. I remember one such patient of the late Dr. Luther Peter's who actually requested enucleation of one eye for her annoying, intractable diplopia. I am happy to say I have had no such case myself, and I know of none that we have had at the Graduate Hospital. As Dr. Tabor has indicated, the cause is not known, but, in addition to the ophthalmological picture, a definite psychogenic factor is probably always present. Since it is human not always to admit one's poor results, it is likely that many such cases are never reported in the literature.

Dr. Gibson, on the other hand, has given us the guiding principles which he has formulated as the result of his experience in the surgical treatment of concomitant (purely horizontal) convergent strabismus. The postoperative corrections he has obtained are so enviable that we can use some of his procedures with a great deal of profit.

He mentioned several points which I feel deserve emphasis. The first is the ideal time for operation. Unfortunately, one sees all too often what he has described as the neglected case, one in which the deviation is of long standing and in which amblyopia is firmly established. In many of these cases the child has reached the age of 6, or even 12, years; in such cases, as he has said, the time of operation is not important, although probably the sooner it is carried out, the better. On the other hand, it is in the early case, one in which esotropia has recently developed, that early operation may be expected to give optimum results. The successful reestablishment of normal binocular function can almost be said to be inversely proportional to the age at which operation is undertaken. In the infant the binocular reflexes are still plastic and not firmly established; therefore, as Dr. Gibson stated, it is in these early cases that the developing sensory mechanism will be of most aid to the surgeon, with his mechanical adjustments.

A second point deserving emphasis is that a refined, differential diagnosis is a prerequisite to success. Conceivably, several different surgical procedures could produce straight eyes in a given case. However, the goal of operative treatment is the restoration of function, not simply a cosmetic improvement. Hence, Dr. Gibson's classification of cases into asymmetrical, monocular and symmetrical binocular involvement can be most helpful in deciding which muscles to attack.

Personally, I have had no experience with marginal myotomy, but Dr. Gibson's arguments in favor of this procedure are logical and his statements very convincing. At the Graduate Hospital, my colleagues and I have been using wholly the recession and resection technics, which Dr. Gibson reserves for his cases of asymmetrical and late convergent strabismus, and we have had no reason to feel disappointed with our results. If the muscle is anchored firmly to the episclera by two or three absorbable surgical sutures, there is little chance for the attachment to slip back; moreover, the method can be used in most early cases. The marginal myotomy, as I understand it, is limited to cases of alternating squints.

There is one other, very minor, point on which I might differ with Dr. Gibson; that is the number of muscles to be operated on at one time. It is ideal to be able to correct a case of strabismus in one operation. Lately, however, I have become more conservative, especially in cases of abnormal retinal correspondence, in which, as Dr. Gibson has pointed out, it is most difficult to estimate the correction, and in those cases in which I suspect that an overcorrection may be likely. If two or three muscles require operation, I confine my efforts to one or two, as the case may be, then wait five or seven days before attacking the remaining muscle. This gives one an opportunity to judge more accurately the correction obtained for each muscle and offers a second chance for final adjustment. Admittedly, this method slightly prolongs hospitalization and subjects the patient to additional anesthesia, but I feel that the ultimate result is to the patient's advantage. As I said, this is a minor point of difference, and is not meant as a criticism.

Dr. I. S. Tassman: I should like to ask Dr. Gibson the difference between the marginal myotomy as he described it and the so-called guarded tenotomy, as performed by others in the past. Was the marginal myotomy done in cases of monocular squint in which the vision was very poor in the affected eye? The results obtained with Dr. Gibson's procedure were very satisfactory in the cases described with a deviation up to 45 degrees. In cases in which I have seen the so-called guarded tenotomy performed, an advancement of some kind was also performed on the opposite muscle.

Dr. Glen Gibson: I should like to thank Dr. Krewson for not taking advantage of the many loopholes that are available in a presentation of this type. I wish that it were possible to be less vulnerable than I am.

In answer to Dr. Tassman, the marginal myotomy is performed as far back on the belly of the medial rectus muscle as one can work, so as to avoid its tendinous portion. This permits the muscle to "give" more, and hence it accomplishes the same result as a recession, without so much danger. It is interesting that it usually gives the right amount of correction. In a tenotomy there is much less relaxation or stretching of the muscle, and the results are less uniform. This procedure is not to be confused with similar procedures which are carried out on the tendon of the medial rectus muscle.

Dr. Tassman's second question was in relation to cases in which the vision differs in the two eyes. This is a crucial point, as it is important that anyone who attempts marginal myotomy understand the problem. If vision is unequal in the two eyes, the operation will not succeed. It requires that the vision be equal, if not normal, in the two eyes before the patient is subjected to the procedure.

Dr. Tassman also asked about the results with deviations up to 45 degrees. A correction for this amount is certainly the maximum that one can obtain by marginal myotomy. It is preferable to apply it to deviations of less degree, particularly those that are variable.

Dr. Tassman mentioned the effect of other muscles. It is vitally important in marginal myotomy that procedures to the lateral rectus are not carried out at the same time, for in so doing one increases the stretch on residual fibers in the muscle.

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Isadore Givner, M.D., *Secretary*

Regular Meeting, April 18, 1949

Use of Air in Cases of Anterior Uveitis: Preliminary Report. DR. JOHN S. CREGAR.

A preliminary report on the behavior of the eye when the contents of the anterior chamber have been replaced with air in cases of anterior uveitis was presented. This procedure was undertaken after observing the tolerance of the eye to aspiration of the aqueous humor and the rapidity of healing following intraocular operations when air is introduced into the anterior chamber, with restoration of the intraocular tissues to approximately their normal relations.

In anterior uveitis the aqueous is abnormal. It may vary physically from a fluid of increased viscosity to a suspension of cells in a fluid or gelatinous medium. It may contain only a few cells in suspension, or it may be entirely filled with pus cells. If such a situation existed elsewhere in any body fluid, drainage would be promptly instituted; but in ophthalmic therapy drainage is the last type of treatment to be instituted. As a result, anterior inflammations of the eye are followed by many complications, such as anterior peripheral synechia, secondary glaucoma, posterior synechia and the formation of membranes over the surfaces bathed with the contaminated aqueous.

The introduction of air was tried in treatment of many forms of inflammation of the anterior segment of the globe, among which were acute iritis, acute iritis with tension, iridocyclitis and uveitis. In all cases in which the first attack was treated no postinflammatory complications were found. The course of the disease was shortened, and the pain was reduced. In cases in which the history showed the present attack to be a recurrence, the episode was reduced in severity, discomfort and duration.

The procedure is performed under the same sterile technic as that which is observed in any intraocular operation. The withdrawal of the aqueous is made by means of a hypodermic needle or by using a small keratome with the incision slightly anterior to the limbus. The size of the hypodermic needle used varies with the nature of the aqueous; i. e., the more viscous or turbulent the fluid, the larger the needle. If there is the suggestion of the cells being clumped or clotted, a keratome is used. The fluid is withdrawn or released from the anterior chamber slowly to avoid the possibility of hemorrhage. This fluid should be sent to the laboratory for cellular study and such other tests as may aid in determining the cause of the initial inflammation. Air is then introduced into the anterior chamber through the same needle, either by replacing the syringe with another or by the method described by Wendell Hughes (*Tr. Am. Ophth. Soc.* **43**: 115, 1945). If a paracentesis has been performed, air is introduced by using the tip of an anterior chamber irrigator or the blunt tip of a lacrimal sac needle. The air used in the cases in this series was not filtered. The amount of air used in each case varied. An amount was introduced sufficient to

distend the anterior chamber to a depth slightly greater than normal. In all cases after the operative procedure was finished, a mydriatic, usually 1 per cent atropine, in ointment form was instilled.

On subsequent observations, it was found that the air was absorbed within two days and that, except in the cases of most violent inflammation or in those in which previous attacks of inflammation had occurred, the aqueous remained clear. In cases in which turbulence of the aqueous or secondary tension appeared the procedure was repeated in four or five days.

This procedure is only an addition to the armamentarium of the ophthalmologist and is not suggested to replace other types of therapy or standard treatments.

Conclusions.—1. In cases of anterior uveitis, it is a safe procedure to drain the anterior chamber of its abnormal contents and to replace these with air.

2. The course of the disease is shortened, and the subjective symptoms are lessened by this type of surgical treatment.

3. The postinflammatory complications of anterior uveitis are reduced in frequency by this procedure.

4. The aqueous is available for laboratory study and may aid in reaching a diagnosis of the etiologic factor.

The Eye-Bank for Sight Restoration, Inc. Dr. R. Townley Paton.

The eye bank has been established in order to make available to hospitals and surgeons who are qualified to perform the corneal transplantation a supply of fresh or preserved corneal tissue, wherever and whenever needed. In brief, the objectives are as follows: 1. The encouragement and extension by teaching and research, of the knowledge and skill required to perform cornea transplantations. Money is needed to extend the horizon of this work.

2. As a subsidiary function, the stimulation of an interest in research on blindness resulting from corneal damage.

3. The establishment of sources of supply of salvaged eyes and corneal tissue, and, through the establishment of the eye bank, the provision of a means for the collection, preparation, storage and redistribution of salvaged eyes and corneal tissue. The total number of eyes received by the eye bank in the period from Feb. 1, 1945 to Feb. 28, 1949 was 1,115. Of this number, 756 were good for transplantation purposes, and 359 were not suitable. The number of laboratory reports sent out on eyes in the same period was approximately 988.

Any eye which is sent to the eye bank will have a complete pathological study, and a report will be sent, on request, to the institution or person who supplied the eye; bacteriologic studies are also made for possible contamination, etc. Institutions desirous of making their own pathological examinations will have the eye returned to them in the proper preservative fluid. There are, of course, many small institutions that do not have the facilities for the proper pathological examination of eyes, and one of the purposes of the eye bank is to encourage complete pathological studies of all eye tissue sent to it.

Lamellar Keratoplasty. Dr. Louis Paufique, Lyons, France (by invitation).

The biologic study of a vast number of corneal diseases reveals that the lesions do not reach the deep layers of the cornea. Contrary to the classic opinion on the matter, it also appears that one can obtain, through a suitable technic, a transparent cornea, without any cicatricial tissue between the graft and the diseased cornea. Histological preparations show this result.

The surgical technic is doubtless more difficult than that of the perforating keratoplasty, but it is easy to practice on eyes from cadavers or animals. In return, it offers the very considerable advantage of exposing the patient to no risks whatsoever, with only simple short postoperative consequences and a very short period of invalidism.

The types of transplants used are (1) the central lamellar graft, from 5 to 8 mm. in diameter, and (2) the total lamellar graft, from 9 to 11 mm. in diameter.

The lamellar transplantation when performed for optical purposes, is recommended in all cases in which the corneal lesions do not affect the posterior layers—in cases of hereditary keratitis of the Haab-Dimmer and Groenouw types; the scars from traumatisms; syphilitic, tuberculous and eczematous keratitis; trachoma, etc. It is the best technic in cases of aphakia with vitreous in the anterior chamber. Statistics covering nearly 250 cases of lamellar keratoplasty prove the advantages of this method.

In addition to its optical role in cicatricial lesions, the lamellar graft is also indicated most frequently in the treatment of chronic or recurring keratitis. For the past eighteen months therapeutic lamellar grafts have been under study. The indications are many: keratitis due to a neurotropic virus; acute or chronic ulcers, even with perforation of the cornea; deep keratitis of various sorts, and recurring pterygiums.

The therapeutic lamellar graft can be either peripheral, with the trophic action of the graft operating on the lesion at a distance, or, in the more serious cases, central or total after excision of the corneal lesions. The results proved to be of paramount interest, and the methods used also offer no danger.

Lamellar transplantation is important as a chief preparatory operation before the perforating keratoplasty in all cases of serious lesions, in which the results are so disappointing, especially vascularized leukomas. A successful lamellar graft in such cases makes possible a successful perforating transplantation in the next few months. It is also one of the best preventive and curative measures in treatment of the graft disease, so common after the perforating transplantation in serious cases. The lamellar graft therefore increases the indications for keratoplasty.

DISCUSSION

Dr. Gerard DeVoe: My comments are based on the pooled material of Dr. Castroviejo and that of the Institute of Ophthalmology. To date, my associates and I at the Institute have assembled 39 cases of lamellar keratoplasty, obviously too small a group on which to base any statistical conclusions. It is also obvious that since our oldest case has been under observation less than a year we are in no position to comment fairly on the results so interestingly presented by Dr. Paufique.

Dr. Castroviejo regrets that previous commitments have made it impossible for him to discuss this paper personally. He has been much interested in the possibilities of lamellar keratoplasty and, as many of you may know, did a considerable amount of experimental work about 15 years ago, only to reach the conclusion that the procedure was an impractical one. The work of the French school has restimulated our interest. Since the work in this country is still in its infancy, we are hesitant to present our findings, in the face of those of our distinguished visitors from France.

I shall summarize our results briefly by noting that, of our patients, eight, or 20 per cent, have to date shown improvement in vision over that existing before operation. The best visual acuity was 20/40, obtained in three patients. Twenty-six patients, or 66 per cent, retain about the same amount of vision that they had before operation. The remaining five patients, or 13 per cent, now have poorer vision than that with which they started.

In general, it has been our experience that the benefits of most lamellar keratoplasties have been virtually nullified by the development of a granular opacification at the base of the graft, often associated with folds and striations in the posterior elastic lamina (Descemet's membrane). Although the anterior part of the graft has frequently remained clear, this clouding at the base, which develops at about the third week in what has previously been a clear graft, has been one of our most distressing problems. In no case have we encountered a perfectly clear, sparkling graft, such as is seen often in the penetrating type of keratoplasty.

In fact, it has been our experience that the results obtained with lamellar keratoplasty are no better than, if as good as, those obtained with superficial keratectomy. Unquestionably the procedure is far safer than penetrating keratoplasty and avoids many unpleasant complications, such as incarceration of the iris, injury to the lens and secondary glaucoma. For that reason, therefore, we feel that lamellar keratoplasty is the procedure of choice for one-eyed persons, patients with aphakia and eyes with small, superficially placed opacities in the pupillary area with good surrounding cornea. In unhealthy, vascularized corneas our results have been poor, all grafts having become cloudy. Neither have we found that a lamellar keratoplasty as a preliminary procedure in preparing a bed for a subsequent penetrating transplant is of great value. We have had little or no experience with this technic as a means of treatment of active corneal disease.

We have been intensely interested in the work of the French school and believe that they have contributed greatly to the advancement of knowledge in the field of keratoplasty. Although our results have not equaled those of Dr. Paufique, we freely admit that our experience has been too limited, both in quantity and in length of follow-up observation, to permit us to evaluate fairly the procedure of lamellar keratoplasty. We shall continue to use the operation and to hope that as our experience increases our results will more nearly approximate those of Dr. Paufique.

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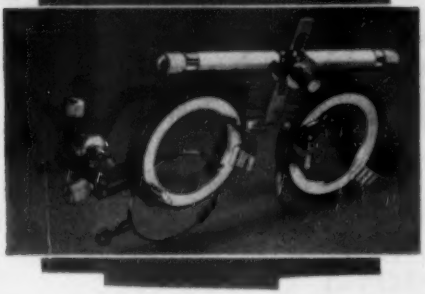

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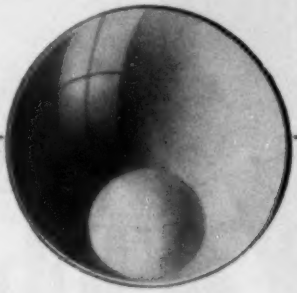

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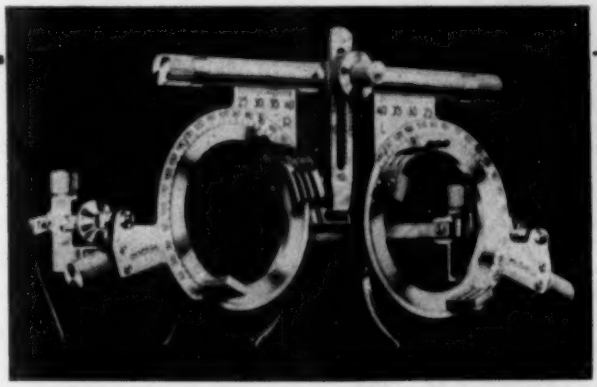

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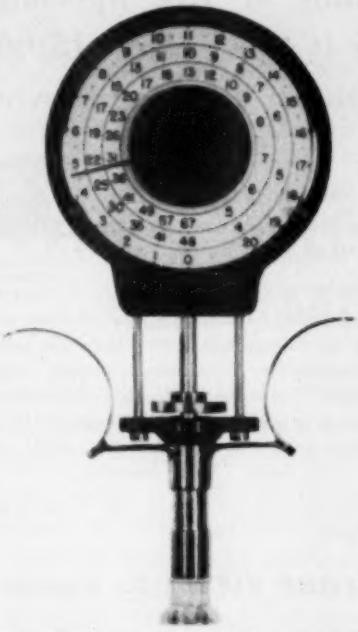

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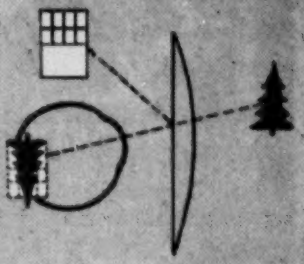

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At infinity, objects to the rear and side can be seen in a mirror even though the reflector is very close to the eye. Because about 4% of the incident light is reflected from each surface of spectacle crown glass, every lens becomes a somewhat inefficient mirror. This explains how some people see faint "ghost" images and may be considerably annoyed if sensitive to them. Lenses of stronger minus or plus powers, where one surface approaches flatness, make particularly good reflectors, as the "ghosts" are often in focus.

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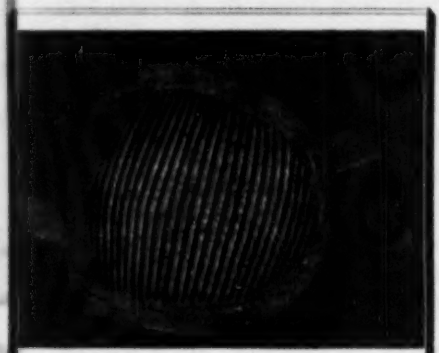

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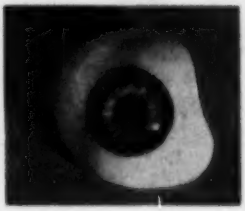

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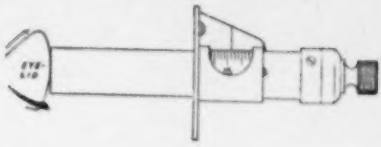

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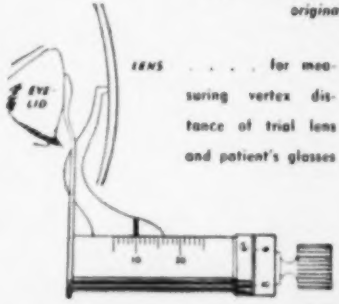

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